Abstract

Reductions in drive and goal-directed behaviour have long been described as key features of schizophrenia. This thesis contains several investigations into the motivational deficits present in people with schizophrenia. Despite not being required for the diagnosis, motivational deficits were found to be a highly prevalent feature of the disease, even among younger patients who were relatively early in their course of illness. Using cross-sectional and longitudinal follow-up study designs, and across two studies with different participants, motivational deficits were found to hold strong predictive value for the determination of functional outcomes. After establishing the importance of motivational deficits in terms of outcomes, underlying behavioural mechanisms were explored using experimental paradigms. Several candidate reward processes were examined concurrently, including valuation of outcomes, estimation of the costs associated with obtaining outcomes, and learning the association between actions and outcomes. Our results provide support for the proposal that individuals with schizophrenia have impairments in their ability to compute effort demands, and that these impairments translate into real-world reductions in goal-directed behaviour. Beyond mechanisms, this thesis also examined the inter-relationship between motivational deficits and another key domain of psychopathology in schizophrenia, namely, cognition. Although these two domains are thought of as distinct, two studies included in this thesis provide empirical evidence of an association, which is interpreted
within a theoretical framework whereby poor motivation translates into reduced effort put forth
during cognitive testing, which ultimately results in poorer submaximal test performance.

Finally, the last study included in this thesis addresses the issue of treatment-induced symptoms.
This study failed to find support for the contention that treatment with antipsychotic medications
necessarily worsens the severity of motivational deficits in schizophrenia. Taken together, these
investigations highlight the importance of motivational deficits in schizophrenia, and lay the
foundation for a mechanistic understanding of these impairments.
Acknowledgments

I have been fortunate to work alongside so many supportive individuals during my graduate studies. First and foremost, I would like to thank Dr. Gary Remington for taking me on as a student all those years ago, and for providing his unwavering support, mentorship, and guidance throughout my training. His faith and continuous encouragement of trainees is unparalleled, and serves as a catalyst for the development of independence, and for this I am truly grateful.

I would also like to thank my program advisory committee members, Drs. Ariel Graff-Guerrero and Konstantine Zakzanis, for their support and feedback, and for challenging me to think critically about my work. I am also grateful to both for the collaborative work we have conducted outside the context of this thesis.

Over the years, I have had the good fortune to work with great collaborators, all of whom deserve a special thanks. Drs. Ofer Agid and George Foussias have been a source of encouragement from the very beginning. I could always count on their thoughtful insights. Gary's reputation has attracted numerous talented individuals to train under his supervision. This, of course, afforded me the unique opportunity to work in a diverse and very intelligent team. I learned a lot from the post-doctoral fellows in the lab (Drs. Patrick McCormick, Hiroyoshi Takeuchi, and Jimmy Lee). Their knowledge and passion for science was inspiring. A special thank you goes to Joshua Lister who began his M.Sc. studies with Gary mid-way through my studies. Josh was a kind and curious person, who always had a smile on his face. His passion for rigorous science was also inspiring; I will not forget our collaborative efforts. His passing was truly tragic - but, he will not be forgotten. I would also like to thank Carol Borlido, Steve Mann and Connie Bartha for being an endless source of information, and always having the answers to my seemingly endless questions. I am also thankful of the help and assistance provided by Sabrina, Liya and Christina.

Outside of the workplace, I am forever grateful to my family for their love and support, without which this thesis would not have been possible. My parents have always encouraged me to pursue my interests in education, and have been supportive throughout. My brother has always been kind, but critical, towards my work. He never ceased to have questions about what I was doing and why! I am immensely grateful for his curiosity in my work. My grandparents have
been nothing short of supportive of all of my endeavors, and I am humbled by their unwavering support. I would also like to thank my many other family members, including my many cousins, and my friends for always expressing interest in my work (even when it sounded boring) and for making the time outside of the lab that much more fun.

Finally, I am thankful to the organizations that have financially supported me in undertaking the work presented in this thesis, including the Government of Ontario (Ontario Graduate Scholarship), the Canadian Institutes of Health Research (Vanier Canada Graduate Scholarship), the University of Toronto's Institute of Medical Science (Entrance Award and Open Fellowship Award), the University of Toronto's School of Graduate Studies (Conference Grant), and the Centre for Addiction and Mental Health's Schizophrenia Division (Travel Award).
Contributions

The studies included as chapters in this thesis are the result of years of collaborative work, thus, for the most part, when discussing the work, I will refrain from using the singular "I" and instead refer to the plural "we." All of the included studies include multiple co-authors. The specific contributions of each author for each of the included studies is outlined here. Notably, though, for each of the studies included in this thesis, I served as the lead investigator and am listed as the first author.

Chapter 3 (Study 1): Gagan Fervaha conceived the idea, designed the study, recruited and tested participants, analyzed the data, conducted the literature search, and wrote the first draft of the paper; George Foussias and Ofer Agid reviewed and edited the paper, and provided expert advice and feedback; Gary Remington supervised all aspects of the study, and reviewed and edited the final paper.

Chapter 4 (Study 2): Gagan Fervaha conceived the idea, analyzed the data, conducted the literature search, and wrote the first draft of the paper; George Foussias, Ofer Agid, and Gary Remington reviewed and edited the paper, and provided expert advice and feedback.

Chapter 5 (Study 3): Gagan Fervaha conceived the idea, designed the study, recruited and tested participants, analyzed the data, conducted the literature search, and wrote the first draft of the paper; George Foussias, Hiroyoshi Takeuchi and Ofer Agid reviewed and edited the paper, and provided expert advice and feedback; Gary Remington supervised all aspects of the study, and reviewed and edited the final paper.

Chapter 6 (Study 4): Gagan Fervaha conceived the idea, designed the study, recruited and tested participants, analyzed the data, conducted the literature search, and wrote the first draft of the paper; Ariel Graff-Guerrero, Konstantine Zakzanis, George Foussias and Ofer Agid reviewed and edited the paper, and provided expert advice and feedback; Gary Remington supervised all aspects of the study, and reviewed and edited the final paper.

Chapter 7 (Study 5): Gagan Fervaha conceived the idea, designed the study, recruited and tested participants, analyzed the data, conducted the literature search, and wrote the first draft of the paper; Ofer Agid, George Foussias, Hiroyoshi Takeuchi, Konstantine Zakzanis and Ariel Graff-
Guerrero reviewed and edited the paper, and provided expert advice and feedback; Gary Remington supervised all aspects of the study, and reviewed and edited the final paper.

Chapter 8 (Study 6): Gagan Fervaha conceived the idea, analyzed the data, conducted the literature search, and wrote the first draft of the paper; Gagan Fervaha, Marcus Duncan, Guy Faulkner and Gary Remington designed the study; Marcus Duncan, George Foussias, Ofer Agid, Guy Faulkner and Gary Remington reviewed and edited the paper, and provided expert advice and feedback.

Chapter 9 (Study 7): Gagan Fervaha conceived the idea, designed the study, recruited and tested participants, analyzed the data, conducted the literature search, and wrote the first draft of the paper; Ofer Agid and George Foussias reviewed and edited the paper, and provided expert advice and feedback; Gary Remington supervised all aspects of the study, and reviewed and edited the final paper.

Chapter 10 (Study 8): Gagan Fervaha conceived the idea, analyzed the data, conducted the literature search, and wrote the first draft of the paper; Konstantine Zakzanis, George Foussias, Ariel Graff-Guerrero, Ofer Agid, and Gary Remington reviewed and edited the paper, and provided expert advice and feedback.

Chapter 11 (Study 9): Gagan Fervaha conceived the idea, analyzed the data, conducted the literature search, and wrote the first draft of the paper; Hiroyoshi Takeuchi, Jimmy Lee, George Foussias, Paul Fletcher, Ofer Agid, and Gary Remington reviewed and edited the paper, and provided expert advice and feedback.
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<tbody>
<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention Deficit/Hyperactivity Disorder</td>
</tr>
<tr>
<td>AD</td>
<td>Anno Domini</td>
</tr>
<tr>
<td>AES</td>
<td>Apathy Evaluation Scale</td>
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<tr>
<td>AES-C</td>
<td>Apathy Evaluation Scale – Clinician Version</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>BARS</td>
<td>Barnes Akathisia Rating Scale</td>
</tr>
<tr>
<td>BC</td>
<td>Before Christ</td>
</tr>
<tr>
<td>BIS-11</td>
<td>Barrett Impulsiveness Scale, 11-item</td>
</tr>
<tr>
<td>BNA</td>
<td>Brief Neurocognitive Assessment</td>
</tr>
<tr>
<td>BNSS</td>
<td>Brief Negative Symptom Scale</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood-Oxygen Level Dependant</td>
</tr>
<tr>
<td>BOS</td>
<td>Behavioural Observation Schedule</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CAINS</td>
<td>Clinical Assessment Interview for Schizophrenia</td>
</tr>
<tr>
<td>CATIE</td>
<td>Clinical Antipsychotic Trial of Intervention Effectiveness</td>
</tr>
<tr>
<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impressions</td>
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</table>
CGI-SCH  Clinical Global Impressions - Schizophrenia
CPZ  Chlorpromazine
CPZ Eq  Chlorpromazine Equivalents
CT  Computed Axial Tomography
dACC  Dorsal Anterior Cingulate Cortex
DAS  Dysfunctional Attitudes Scale
DBS  Deep Brain Stimulation
DLPFC  Dorsolateral Prefrontal Cortex
DSM  Diagnostic and Statistical Manual of Mental Disorders
DSM-IV-TR  Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text-Revision
DSM-5-SS  Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Clinician-rated Dimensions of Psychosis Symptom Severity
DTI  Diffusion Tensor Imaging
DUI  Duration of Illness
ECT  Electroconvulsive Therapy
EBS  Emotional Blunting Scale
fMRI  Functional Magnetic Resonance Imaging
GABA  γ-aminobutyric acid
HC  Healthy Control
HE/HR  High Effort/High Reward
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>IAPS</td>
<td>International Affective Picture System</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IMPS</td>
<td>Inpatient Multidimensional Psychiatric Scale</td>
</tr>
<tr>
<td>IMPS-Neg</td>
<td>Inpatient Multidimensional Psychiatric Scale Negative Symptoms</td>
</tr>
<tr>
<td>LARS</td>
<td>Lille Apathy Rating Scale</td>
</tr>
<tr>
<td>LE/LR</td>
<td>Low Effort/Low Reward</td>
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<tr>
<td>MacCAT</td>
<td>MacArthur Competence Assessment Tool</td>
</tr>
<tr>
<td>MASS</td>
<td>Motor-Affective-Social Scale</td>
</tr>
<tr>
<td>MATRICS</td>
<td>Measurement and Treatment Research to Improve Cognition in Schizophrenia</td>
</tr>
<tr>
<td>MCCB</td>
<td>Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery</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>MINI-Plus</td>
<td>Mini International Neuropsychiatric Interview, Plus Edition</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NAc</td>
<td>Nucleus Accumbens</td>
</tr>
<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
</tr>
<tr>
<td>NSA</td>
<td>Negative Symptom Assessment</td>
</tr>
<tr>
<td>NSRS</td>
<td>Negative Symptom Rating Scale</td>
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</table>
OFC     Orbitofrontal Cortex
PANSS  Positive and Negative Syndrome Scale
PAS    Physical Anhedonia Scale
PET    Positron Emission Tomography
PFC    Prefrontal Cortex
PNS-Q  Positive and Negative Symptoms Questionnaire
QLS    Quality of Life Scale
QLS-A  Quality of Life Scale - Abbreviated Version
RDoC   Research Domain Criteria
rTMS   Repetitive Transcranial Magnetic Stimulation
SANS   Scale for the Assessment of Negative Symptoms
SAPS   Scale for the Assessment of Positive Symptoms
SAS    Simpson-Angus Scale
SCID-II Structured Clinical Interview for DSM-IV Disorders – Axis II
SCZ    Schizophrenia
SD     Standard Deviation
SDS    Schedule for the Deficit Syndrome
SDSS   Subjective Deficit Syndrome Scale
SE     Standard Error
SEDS   Subjective Experience of Deficits in Schizophrenia
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>SHAPS</td>
<td>Snaith-Hamilton Pleasure Scale</td>
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<tr>
<td>SNS</td>
<td>Self-Evaluation of Negative Symptoms</td>
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<tr>
<td>SOFAS</td>
<td>Social and Occupational Functioning Assessment Scale</td>
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<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
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<td>SPQ</td>
<td>Schizotypal Personality Questionnaire</td>
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<td>SSA</td>
<td>Scale for Social Anhedonia</td>
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<td>VMPFC</td>
<td>Ventromedial Prefrontal Cortex</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHO/PIRS</td>
<td>World Health Organization Psychological Impairments Rating Schedule</td>
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Chapter 1

1    Introduction and Literature Review

1.1    Schizophrenia

1.1.1    A Historical Account

Insanity has plagued mankind for centuries. While descriptions of madness are ample throughout time, these have been varied, suggesting that the nature and causes of insanity are multifold - i.e., that there exist multiple forms for mental illness (1-3). Some forms of insanity are better illustrated in ancient texts than others; accounts of affective disorders (e.g., melancholia) are relatively well-documented in ancient times (4, 5), whereas the mere existence of convincing cohesive descriptions of schizophrenia in classical antiquity is debated (6-11). Several proposals for this relative absence have been advanced, including the notion that historically mental illness may have fallen under the purview of religion rather than medicine (7, 12). Beyond the concept of schizophrenia per se, there are certainly documented descriptions of clinical features associated with the illness. Some of the earliest descriptions emerge from times dating back to the third millennium BC, where cuneiform tablets from ancient Mesopotamia document individuals who were persecuted by mischief-makers and resorted to witchcraft, spells, magic or "other evil machinations," and were treated by way of cultural rituals (7). Later writings from Hindu texts in ancient India describe individuals who were possessed by demons and as a result, manifested poor hygiene, behavioural disorganization, poor memory, and movement abnormalities (7, 8). Historical accounts of schizophrenia-like experiences were also documented in ancient Greece and Rome, and included descriptions of hallucinations, behavioural disorganization, and delusions (7); for example, in the 6th century AD, Alexander of Tralles details a case of a woman who believed the fate of the entire world literally resided on the position of her finger, and that bending this finger would destroy the world (7). Similar descriptions of hallucinatory experiences, delusions, disorganization, impairments in thinking, and social functioning were described in ensuing years; however it is notable that each case presented with a unique combination of symptoms. By the 17th century AD, more systematic descriptions of cases that parallel contemporary notions of schizophrenia were presented. For
instance, there were descriptions of individuals who experienced bizarre delusions involving having morphed into an animal (e.g., lycanthropy) which lasted for months to years, as well an autobiography of a young minister from England who experienced paranoid delusions and auditory hallucinations, which persisted for months (7). During this period of time, Thomas Willis distinguished foolishness from stupidity, which when mapped onto current nosology and terminology seems to differentiate schizophrenia from intellectual disability (i.e., mental retardation) (7, 13). It is notable that these early descriptions of putative schizophrenia-like experiences are varied, with each case presenting a distinct combination of symptoms and with varying themes of psychosis.

It was in the 19th century that the foundations of the schizophrenia disease concept, as currently applied, were formalized. This important advance is credited to Emil Kraepelin who proposed a singular diagnostic entity termed dementia praecox to explain cases that he followed or reviewed presenting with psychosis and disorganization that began in adolescence or adulthood and resulted in chronic mental deterioration (14, 15). Kraepelin's genius was in amalgamating previously described conditions of catatonia and hebephrenia, with a novel description of dementia paranoides (i.e., paranoid schizophrenia) into a singular nosological category (15). In grouping these previously distinct conditions, Kraepelin deemphasized the notion of a single pathognomonic symptom, and instead emphasized a focus on the full clinical picture; however, Kraepelin considered poor outcome as characteristic of all patients with dementia praecox. Importantly, Kraepelin also distinguished dementia praecox from manic-depressive insanity (i.e., bipolar disorder), based on differences in course and outcome (14, 16), a distinction that still holds in contemporary nosology (17, 18). While Kraepelin employed the term dementia praecox to connote a singular diagnostic entity, he was not the first to use it. Decades earlier, Benedict Morel was among the first to use the term demence precoce to describe cognitive deficits among young patients (19). Similar to Kraepelin's dementia praecox, Thomas Clouston proposed the concept of "adolescent insanity" and emphasized course and prognosis for diagnostic purposes (20). The term schizophrenia (i.e., the English translation of the German schizophrenien) was coined in 1908 by Eugen Bleuler (21, 22). Bleuler built on the dementia praecox concept but importantly also made several substantial conceptual changes, which warranted a novel term. Similar to Kraepelin, his conceptualization of the disorder was based on detailed clinical observations. However, in contrast to Kraepelin, and perhaps related to his personal experience
with the patients he followed, he envisioned a disorder with greater heterogeneity in terms of prognosis - not all patients would follow a course of chronic deterioration (23, 24). To this end, Bleuler explicitly acknowledged the illness' heterogeneity by not referring to the singular concept of schizophrenia; instead, he referred to the group of schizophrenias (23). His decision to employ the term schizophrenia for revising Kraepelin's concept of dementia praecox was not only to de-emphasize the previously inevitably poor prognosis associated with the diagnosis, but also to propose that the dissolution of psychic functions was central to the illness' conceptualization (22, 23). While Bleuler emphasized the schizophrenias as a group of (inter-related) disorders, most ensuing work has examined schizophrenia as a singular construct, albeit with some investigations of subgroups of patients parsed using various criteria (e.g., symptom presentation). It is also notable that the concept of schizophrenia has evolved since these original descriptions, and patients considered to have the disease under one classification scheme may not be considered the same under others (25, 26).

1.1.2 Diagnosis and Spectrum Disorders

The diagnosis of schizophrenia is rooted in phenomenology, and relies on clinical observation of specific signs and symptoms. This tradition dates back to Bleuler's description of fundamental (i.e., characteristic of schizophrenia in particular) versus accessory symptoms (i.e., those shared with other disorders), and primary (i.e., directly related to the core pathology underlying schizophrenia) versus secondary symptoms (i.e., those related to the primary insult, but are not core in and of themselves) (23, 27-29). While many texts routinely suggest that Bleuler emphasized affect, associations, autism, and ambivalence (i.e., the so-called 4 A's) as fundamental to schizophrenia, and therefore its diagnosis, it should be noted that he did not see each of these symptoms as primary (23, 27, 29).

Following the tradition of Kraepelin and Bleuler, early systematic efforts to diagnose schizophrenia patients (e.g., the 1st edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM]) lacked strict operational criteria, and instead relied heavily on clinicians' overall impression and had strong psychoanalytical and psychodynamic influences (30, 31). Unsatisfied with the reliability of this approach, particularly for research purposes, investigators turned their attention to developing and refining operational criteria for the diagnosis of
schizophrenia. For example, Kurt Schneider in his attempt to delineate pathognomonic "first-rank" symptoms of schizophrenia focused on positive psychotic symptoms (e.g., auditory hallucinations with voices commenting on behaviour) (32, 33). Several other criteria were proposed to accurately and reliably categorize schizophrenia cases (34-37). Empirical efforts also exist which have attempted to discern clinical symptoms that discriminate those classified as having schizophrenia versus those with other mental disorders (e.g., mood disorders) (33). These studies have generally agreed that no single sign or symptom, or even constellation of symptoms, is pathognomonic of schizophrenia. But what did become clear was that symptoms such as delusions and hallucinations could be assessed and ascribed to schizophrenia more reliably than could symptoms such as lack of drive and affective flattening (i.e., the so-called negative symptoms) (35).

While a pathognomonic sign or symptom of schizophrenia remains elusive, the creation of operational criteria has undoubtedly improved the reliability of the diagnosis of schizophrenia (38). It is therefore not a surprise that such operational criteria were adopted by later revisions of the DSM (i.e., DSM-III) (39, 40). It should be noted here that while operational criteria improved the reliability of establishing a diagnosis of schizophrenia, the issue of validity of the diagnosis still remained (41); in other words, the question of whether the diagnosis implies a single disease (i.e., schizophrenia) or whether it connotes a number of diseases (i.e., the schizophrenias) remains open to debate.

Current diagnostic criteria for schizophrenia, including those outlined in the DSM and the International Classification of Diseases (ICD), focus on the presentation of symptoms, their persistence over time, functional consequences, and exclusion of competing disorders that might account for the development of symptoms. The diagnostic criteria for schizophrenia outlined in DSM-IV-TR (i.e., the text-revision of the 4th edition of the DSM) (42) are outlined below; it should be noted that a newer iteration of the DSM has been recently published, DSM-5 (17), however, the changes in criteria are minimal except for the exclusion of the note under criterion A (43). While the emphasis on diagnosis is clearly related to symptoms of psychosis, it is notable that negative symptoms (i.e., affective flattening, alogia, and avolition) are explicitly embraced in the diagnostic criteria, highlighting their importance. However, it could also be argued that placing positive psychotic symptoms at the fore, as defining features of schizophrenia, represents a point of departure from Kraepelin and Bleuler's original descriptions of the illness (26). For
reference, a full description of an individual with schizophrenia has been published previously (44), as have descriptions of specific symptoms experienced by several cases (45).

Table 1-1. DSM-IV-TR criteria for the diagnosis of schizophrenia

<table>
<thead>
<tr>
<th>A. Characteristic symptoms:</th>
<th>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>
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<tr>
<td>(1) delusions</td>
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<td>(2) hallucinations</td>
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<td>(3) disorganized speech (e.g., frequent derailment or incoherence)</td>
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<td>(4) grossly disorganized or catatonic behavior</td>
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<tr>
<td>(5) negative symptoms, i.e., affective flattening, alogia, or avolition</td>
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<td>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 thought, or two or more voices conversing with each other</td>
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| 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 during 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).

Note: These criteria have been reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Copyright 2000, American Psychiatric Association. (42)

The diagnostic criteria for schizophrenia require the absence of a substantial overlap between the active-phase symptoms of schizophrenia and symptoms of a mood disorder (e.g., depression, mania). There does, however, exist a subset of patients though who would otherwise meet criteria for schizophrenia but they also experience concurrent mood symptoms. These individuals presumably have an admixture of schizophrenia and affective illness, rather than having the two illness exist in a co-morbid fashion, and therefore a separate diagnostic category has been proposed and developed to parse this group of patients (i.e., schizoaffective disorder) (42). Several investigations have been undertaken to determine whether patients with schizoaffective disorder are truly distinct from those with either schizophrenia or affective illness (e.g., bipolar disorder), and further, whether these patients align more closely with the diagnosis of schizophrenia or affective illness (46-61); these studies generally support the notion that individuals with schizoaffective disorder align more with those with schizophrenia versus those...
with affective illness, but their presentation, course and underlying deficits are often found to be lesser in severity than those with schizophrenia proper. Taken together, schizoaffective disorder is considered a schizophrenia-spectrum condition, and as such is listed under the schizophrenia spectrum diagnostic chapter in the most recent revision of the DSM (17). Schizoaffective disorder is mentioned explicitly here as many of the contemporary investigations into the phenomenology and behaviour of patients with schizophrenia, including works detailed in the latter part of this chapter and in the subsequent chapters, explore these issues in a combined sample of schizophrenia and schizoaffective disorder patients.

Table 1-2. DSM-IV-TR criteria for the diagnosis of schizoaffective disorder

| A. | An uninterrupted period of illness during which, at some time, there is either a Major Depressive, Manic, or Mixed Episode, concurrent with symptoms that meet Criterion A for Schizophrenia. Note: The Major Depressive Episode must include depressed mood. |
| B. | During the same period of illness, there have been delusions or hallucinations for at least 2 week in the absence of prominent mood symptoms. |
| C. | Symptoms that meet criteria for a Mood Episode are present for a substantial portion of the total duration of the active and residual periods of the illness. |
| D. | 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. |

*Specify type:*

*Bipolar type:* if the disturbance includes a Manic or Mixed Episode (or a Manic or a Mixed Episode and Major Depressive Episodes)

*Depressive type:* if the disturbance only includes Major Depressive Episodes.
The diagnosis of schizophrenia and schizoaffective disorder both hinge on the presence of an episode of psychosis, as well as some additional criteria. However, while the presence of psychosis is not difficult to establish, the establishment of a diagnosis of schizophrenia or schizoaffective disorder versus another disorder with the presence of psychosis is less straightforward. This is the case as psychosis is present in a number of other disorders (17, 62). Accurate diagnosis becomes especially difficult immediately following the first-episode of psychosis, where diagnostic stability is less than ideal, and routinely changes as the illness evolves and more clinical information becomes available (63-70).

Table 1-3. Diagnostic categories of psychotic disorders

- Non-affective psychotic disorders:
  - Schizophrenia
  - Schizoaffective disorder
  - Schizophreniform disorder
  - Delusional disorder
  - Brief psychotic disorder
  - Psychotic disorder not otherwise specified

- Affective psychotic disorders:
  - Bipolar disorder with psychotic features
1.1.3 Epidemiology

Individuals develop schizophrenia across the globe (71). While the incidence of the disorder is relatively low (median value of 15.2 per 100,000 persons per year; 10%-90% quantile values of 7.7-47.0) (72), the relative burden of the disorder is high (73, 74). Notably, the incidence of the disorder is higher for males, individuals who have migrated, and those living in urban regions (72). The median point prevalence of schizophrenia has been reported to 4.6 per 1,000 persons (10%-90% quantile values of 1.9-10.0), while the median lifetime morbid risk for the disorder is 7.2 per 1,000 persons (10%-90% quantile values of 3.1-27.1) (75). The prevalence rates have been found to be lower in native-born individuals compared to migrants, and among the "least developed" regions of the world (75). Notably, prevalence rates are higher if other schizophrenia-spectrum conditions are included (76, 77). While the prevalence of schizophrenia is relatively lower than that of other psychiatric disorders, schizophrenia ranks highest among all mental and substance use disorders in terms of individual burden (73); it is therefore not very surprising that the disorder had been described as being "arguably the worst disease affecting mankind, even AIDS [Acquired Immune Deficiency Syndrome] not excepted" (78).

Patients with schizophrenia are also at greater risk of pre-mature death compared to persons in the general community (median standardized mortality ratio of 2.6; 10%-90% quantile values of 1.2-5.8) (79). This increased rate of mortality includes a greater risk of death by suicide, but even when such cases are excluded the risk remains higher than the general population (79-81). Individuals with schizophrenia also harbor an increased risk of developing a host of co-morbid medical conditions such as metabolic syndrome (82, 83) and type 2 diabetes mellitus (84, 85). Rates of substance abuse and substance use disorders are also higher in patients with

- Major depressive disorder with psychotic features
- Psychotic disorder due to a general medical conditions
- Substance-induced psychotic disorder

Note: These diagnostic categories are based on nosology outlined in DSM-IV-TR (42)
schizophrenia relative to the general population (86-88). On the other hand, risk for certain conditions such as some cancers appears to be lower among patients with schizophrenia (89-91).

### 1.1.4 Risk Factors

Several factors that increase an individual's relative risk of developing schizophrenia have been identified; however, no single factor is necessary and sufficient for predicting schizophrenia. The single best predictor of schizophrenia risk is a positive family history of the disorder (92). Numerous studies have been conducted examining the heritability of schizophrenia (93-104), and these have generally concluded that an individual's relative risk for schizophrenia increases with increasing genetic closeness (e.g., risk for monozygotic twins is higher than risk for other 1st degree relatives, which in turn is higher than the risk for 2nd degree relatives) (92). The mechanisms underlying this familial risk for schizophrenia involve both genetic and environmental factors. In search of the genetic causes of schizophrenia, several investigations have been conducted and implicate a host of genes and genomic abnormalities (105-114). Most recently, a large-scale study with 36,989 schizophrenia cases and 111,075 controls evaluated across the world, found evidence for 108 independent loci that conferred risk for the disorder, albeit the absolute risk for any one locus was modest (115). That is, no single gene has been found to be necessary or sufficient for the disorder; rather, it seems that many genes independently and with small effect sizes increase risk (116). The genes implicated are involved in a host of biological processes including neural development and immune system functioning (115).

Numerous environmental factors have also been implicated in the risk for schizophrenia. Environmental risk factors for schizophrenia include several prenatal and perinatal factors such as prenatal maternal infection (117, 118), maternal stress during pregnancy (119), and obstetric complications (120-126). Advanced paternal age has also been suggested as a risk factor for the development of schizophrenia (127-129), as has poorer parental socioeconomic status (130). Being born in winter months also seems to confer a small risk for developing schizophrenia (131, 132). Several environmental exposures experienced during childhood have also been implicated in the risk for schizophrenia such as early parental loss (133), trauma (134, 135), and head trauma (136, 137). The use of cannabis during adolescence has as well been advanced as a risk
factor for developing schizophrenia (138-142). Social factors such as an upbringing in an urban environment (143) and migration (144-146) have also been documented as increasing the relative risk for developing schizophrenia.

Studies on the potential risk factors of schizophrenia span many decades, and have seen multiple shifts in focus. For example, a once prominent theory of the "schizophrenogenic mother" as a major precipitant for the development of schizophrenia (147, 148) has now been refuted and abandoned (149). The idea that multiple risk factors may contribute to the risk for schizophrenia in an additive manner has also been proposed; for example, it is possible that risk factors present during early development render the central nervous system more prone to subsequent risk factors in early adolescence (150). In the past few decades there has been an increased impetus into examining multiple interactions between risk factors, including interactions between genetic and environmental factors (151-153). Furthermore, there have been some investigations examining risk factors for specific subgroups of patients (154-156).

1.1.5 Course and Outcomes

The diagnosis of schizophrenia is made following the presence of an episode of psychosis. The subsequent course however differs for each patient, with some experiencing only a single episode followed by relative recovery, and others following a more chronic course marked by relapses and poor functioning (157-167). It is notable that many patients do well despite a diagnosis of schizophrenia; however, these individuals represent the minority of those with the diagnosis (168-185). It is estimated that less than 20% of patients evidence periods of sustained symptom control coupled with adequate psychosocial functioning, and therefore considered, by some definitions (186-188), to be "recovered" (185).

There are several antecedents of schizophrenia that exist long before a formal diagnosis is justified. These include subtle signs and symptoms present in childhood such as motor abnormalities, cognitive dysfunction and social deficits (59, 189-197). Also predating the onset of frank psychosis, and thus formal diagnosis of schizophrenia, there exists a prodromal period marked with subclinical symptoms and functional deterioration (198-200). Individuals in the putative prodrome present with a myriad of symptoms including cognitive impairments,
reductions in drive and motivation, depressed mood, anxiety, social withdrawal and suspiciousness to name a few (199). These symptoms usually last for several years, during which time psychosis evolves (201). There is a notable delay from the onset of frank psychosis to individuals receiving care, which is typically referred to as the "duration of untreated psychosis" (202), and this has been shown across several studies to be a determinant of poor outcomes (203-207).

Figure 1-1. An illustration of the natural history and course of schizophrenia

The figure illustrates one potential trajectory of illness of an individual with schizophrenia. The various phases of illness, their corresponding phases of development and notable domains of psychopathology are shown. This figure was adapted from previous work (201, 208).

The optimal outcome for schizophrenia is now embraced as multidimensional, much like the nature of schizophrenia itself, and includes remission of symptoms, adequate social and vocational functioning, and a sense of subjective well-being (209). Prospective studies of first-episode schizophrenia patients have noted that the longitudinal outcome of schizophrenia is heterogeneous across individuals, with "good" outcomes in less than half of those with diagnosis
and, similarly, "poor" outcomes in less than half of patients, with the remaining patients somewhere in-between (210, 211). These descriptions of heterogeneity in the course and outcome of schizophrenia patients stand in contrast to historical descriptions of the illness, most notably from that of Kraepelin's dementia praecox (14). As an aside, the historical influence of Kraepelin's vision of a poor prognosis characterizing schizophrenia has not disappeared from contemporary literature, with several investigations examining the characteristics of schizophrenia patients with particularly poor outcomes who are said to have the Kraepelinian subtype of schizophrenia (212-218).

While most patients do not achieve optimal outcome in harmony, several do achieve one or another milestone (e.g., symptomatic remission alone) (172-183). That is, many patients continue to experience poor functional outcomes in the face of good clinical outcome (i.e., symptom remission). With regards to functional outcome in particular, the prognosis is somewhat more dim than that of clinical symptoms, and this may relate in part to social and cultural issues. For example, receipt of social assistance has been hypothesized to serve as a disincentive for taking up employment among individuals with schizophrenia (219). Regardless, the rate of competitive employment among patients with schizophrenia is strikingly low, with estimated rates of less than 15-20% of patients engaged in part-time or full-time work (74, 219-221). Even in first-episode samples, less than 50% of individuals with schizophrenia-spectrum disorders are employed or in school (177, 222-224). This rate of unemployment is notable as it is a significant contributor to the total societal burden and cost associated with schizophrenia (74, 225, 226).

1.1.6 Treatment

Current guidelines suggest antipsychotic medications as the cornerstone of treatment for schizophrenia, highlighting early and continuous use (227-231). The discovery of the efficacy of these medications was serendipitous, as has been the case for many psychiatric drugs (232). In 1951, chlorpromazine was utilized for its anesthetic properties in surgical patients, and based on its calming properties was subsequently employed by Hamon and colleagues and separately by Delay and colleagues, both in Paris, who described the efficacy of this compound in treating psychiatric patients (233-235). The discovery of chlorpromazine's antipsychotic activity and efficacy for treating psychiatric patients heralded a new era of biological psychiatry. Attention
soon turned to discerning the mechanisms by which chlorpromazine and related drugs exerted their effects. Ensuing pre-clinical work pointed towards the dopaminergic system as a common target of these drugs, and in particular antagonism at the dopamine D2 receptor (236-241). In one of the more elegant studies, Seeman and colleagues demonstrated that an antipsychotic drug’s affinity for the dopamine D2 receptor was directly proportional to the treating dose of the drug routinely used in the clinic (238). Later work employing in vivo neuroimaging techniques such as Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) in patients with schizophrenia further suggested that dopamine D2 receptor antagonism may be the common link between effective antipsychotic medications; taken together, the evidence positioned this as the central mechanism of action for these medications (242-244).

On the heels of the success of chlorpromazine, initiatives were undertaken to develop similar compounds for the treatment of psychosis and schizophrenia. Over the decades, numerous effective antipsychotic medications have emerged, all with similar efficacy, but differing to some degree in their side effect profiles (245). Specifically, older medications (i.e., first-generation or typical agents) are associated with greater motor side effects, while newer medications (i.e., second-generation or atypical agents) are associated with lower risk for motor side effects but greater propensity towards metabolic disturbances. The exact definition of “atypicality” is debated but seems to have emerged with the use of clozapine, and is predicated on lower risk for extrapyramidal side effects (244, 246-249). Following their introduction into the market, there was enthusiasm for the so-called second-generation antipsychotic drugs having increased efficacy and, at the same time, decreased propensity of side effects, at least in terms of motor system dysfunction. However, evidence from large-scale effectiveness trials and meta-analyses has not been consistent or robust in supporting the superiority of atypicals and, instead, suggests that as a class atypical agents are not more effective than typical agents (250-256). A notable exception is clozapine which stands alone as the most effective drug for the treatment of patients who have failed to respond adequately to previous antipsychotic trials, and are therefore considered treatment-resistant (257-260). There exists a certain proportion of patients who fail to respond adequately to antipsychotics, a subgroup comprising of up to one-third of all patients (261-264). Of note, it has been suggested that patients with schizophrenia who respond to
antipsychotic medications are distinct from those who are treatment-resistant, with each possibly reflecting a subtype of schizophrenia encompassing different pathophysiology (265).

While contemporary antipsychotic randomized controlled trials employ a global measure of overall symptom burden of schizophrenia as a primary outcome in schizophrenia, it has become increasingly apparent that the focus of antipsychotic drugs is just that (i.e., anti-psychosis, rather than anti-schizophrenia in general). In fact, clinicians' global impression of illness severity in schizophrenia and its change following antipsychotic treatment is most closely associated with the positive psychotic symptoms of the illness (266-269). Moreover, antipsychotics seem to exert their greatest influence, in terms of effect size of symptom reduction, on positive psychotic symptoms (270). Antipsychotics are less effective for other domains of illness (e.g., cognitive impairments, loss of drive) (270-273), resulting more recently in efforts to develop novel pharmacological agents targeting these important other symptoms domains. However, to date no drug has met with success (274-278).

Non-pharmacologic strategies in combination with ongoing antipsychotic treatment have also proven effective for the treatment of schizophrenia. A range of psychosocial interventions have been developed and shown to be effective across a number of measures including reduction of symptom severity and relapse rates, enhanced adherence, as well as improvement of community functioning (279-283). These include assertive community treatment, cognitive behavioural therapy, cognitive remediation, family psychoeducation, illness self-management training, social skills training, and supported employment (282, 284). Beyond psychosis, some of these strategies have also been shown to be effective for other illness domains. For example, in a combination approach, Kane and colleagues developed and delivered a multi-pronged approach to first-episode care that involved pharmacotherapy, family psychoeducation, individual therapy and supported employment, reporting positive effects in terms of community functioning and quality of life (285). In terms of more specific therapies, cognitive remediation has shown promise for aiding in the reduction of cognitive impairments (286-288). Some early work has also demonstrated the potential efficacy of various forms of cognitive therapy for reducing negative symptoms (289-294).

Neuromodulation studies have also been conducted to examine the efficacy of these for the treatment of schizophrenia. Electroconvulsive therapy (ECT) has demonstrated efficacy for the
treatment of positive psychotic symptoms in schizophrenia, especially in treatment-refractory cases (295-299). The results of trials examining the efficacy of repetitive transcranial magnetic stimulation (rTMS) to the temporoparietal cortex for the treatment of resistant psychosis, mainly relating to hallucinatory experiences, in schizophrenia have been mixed, and have generally not supported this approach (300-305). There have also been some mixed studies examining the efficacy of rTMS for cognitive and negative symptoms (306-311). To date, there have been no trials examining deep brain stimulation for the treatment of schizophrenia.

1.1.7 Pathophysiology

There is no reliable and proven pathophysiological mechanism underlying schizophrenia that has withstood the test of time, at least not one that characterizes all patients with the diagnosis. Instead, there are only theories. For the most part, these come from neuropathological investigations including a variety of methodologies, as well as the existing knowledge of the relationship between neural circuitry and behaviour. Perhaps the longest standing hypothesis for the pathophysiology underlying schizophrenia emerged from the discovery of antipsychotic medications and their putative mechanism of action, specifically the dopamine hypothesis. The dopamine hypothesis finds support from studies demonstrating that antipsychotic medication reduce dopaminergic functioning, as well as studies showing substances that enhance dopaminergic functioning induce or exacerbate psychosis (312-315). In line with this theory, recent meta-analytic studies examining patient-control differences in PET markers related to dopamine have reported increased presynaptic dopamine functioning in patients with schizophrenia (316-318). Not all patients with schizophrenia demonstrate this abnormality, though, and recent investigations have begun to examine clinically defined subgroups of patients who do and do not manifest this pathophysiological deficit (319).

While the dopamine hypothesis has its roots in subcortical mesolimbic functioning and its links to positive psychotic symptoms, revisions of this hypothesis have additionally incorporated prefrontal functioning and circuit abnormalities that may also account for other symptom domains present in the illness (e.g., cognitive impairments, loss of drive) (320-324). Beyond dopamine, other neurochemical systems have also been implicated. For example, several investigations have pointed toward glutamate dysfunction in the pathophysiology in
schizophrenia (325-330), while others have suggested a key role for dysfunction in γ-aminobutyric acid (GABA) neurotransmission (331-335).

At the turn of the 20th century neuropathological insights into schizophrenia were scant, conflicting, and did not reveal large lesions (336), which contributed to some disappointment in the field. In fact, the absence of tractable neuropathological findings in schizophrenia, has led some investigators to describe this illness as the "graveyard" of neuropathologists (337). However, later work with post-mortem brains of schizophrenia began to uncover several replicable findings (338, 339).

Early in vivo neuroimaging studies using computerized axial tomography (CT) imaging of the brains of patients with schizophrenia found macroscopic abnormalities, with the main finding being that of enlarged lateral ventricles (340-344). These early CT findings of ventricular enlargement were largely replicated in later years using magnetic resonance imaging (MRI) (336). Owing to the greater anatomical resolution afforded by MRI, and the fact that neuropathological changes in schizophrenia are relatively subtle, studies began to also identify other brain regions that differed between patients and controls. These include diffuse regions in the brain, including structures within the medial temporal lobe, superior temporal gyrus, frontal lobe, and parietal lobes (336, 345, 346). Later meta-analyses confirmed that abnormal grey matter findings (i.e., abnormalities) were distributed throughout the brain and affected several regions, including anterior cingulate cortex (ACC), insula, and thalamus to name but a few (347-352). Building on the evidence of nodes in the brain being abnormal, several studies have employed diffusion tensor imaging (DTI) as a means to quantify the fidelity of white matter tracts that connect brain regions. These studies have revealed a host of white matter tract-related abnormalities, including dysconnectivity within frontolimbic circuits (353-355). These results provide support for those theories positing schizophrenia to be a disorder related to neural dysconnectivity (356-361).

Abnormalities in brain structure, coupled with changes in neurochemical composition and functioning, should, at least in theory, give rise to functional alterations within the neural networks of patients with schizophrenia. Functional MRI (fMRI) studies have demonstrated just this. However, before mentioning these, it should be noted that just as with structural MRI, there exist several caveats in the interpretation of functional imaging findings, many of which have
been detailed in the literature (362-364); as such, only a few replicated hypothesis-driven findings have been reported, and thus far no single finding has demonstrated clinical value. With this in mind, several meta-analytic studies examining fMRI studies using various tasks to elicit responses have revealed abnormal activity patterns in a range of brain areas including the dorsolateral prefrontal cortex (DLPFC), dorsal ACC (dACC), and amygdala to name a few regions (365-371). These investigations have revealed both hypo- and hyper-activation patterns in response to stimuli, possibly reflecting both under-recruitment of appropriate brain regions and over-recruitment and reliance on compensatory mechanisms. One finding that stands out and has been replicated is the relative lack of effective engagement of the DLPFC cortex in response to cognitive demands (i.e., hypofrontality) (372-375). However, even this notion has been further refined and, instead of hypofrontality per se, evidence suggests a compromise between performance and neural efficacy (376). Furthermore, and in line with the direction of DTI studies, several fMRI studies have moved beyond findings of regional activity pattern abnormalities toward investigations of aberrant functional network organization, dynamics, and processing efficiency (377-381).

While some studies have noted an influence of antipsychotic medication on MRI findings (382-385), abnormal MRI findings have also been consistently found in first-episode antipsychotic-naïve individuals (351). Longitudinal MRI studies have shown that over time patients with schizophrenia evidence a decline in grey matter volumes indexed via MRI, and this has been taken to possibly reflect evidence for progressive deterioration and evolution of the illness (386-399). However, this position has been challenged given the concomitant influence of relapse, substance use, and antipsychotic medications on longitudinal MRI signal changes (400). The current prevailing view is that schizophrenia is a disorder of neurodevelopment (322, 401-409). Viewing schizophrenia as a neurodevelopmental versus neuroprogressive disorder emphasizes aberrant brain maturational processes during adolescence rather than chronic continuous deterioration (410).

### 1.1.8 Signs and Symptoms

Many of the signs and symptoms associated with schizophrenia have been mentioned in the preceding text, either as individual symptoms (e.g., auditory hallucinations) or clusters (e.g.,
positive psychotic symptoms). These will be described and discussed in greater detail in this section. While individual symptoms are certainly important for our understanding of the diagnosis, prognosis, and underlying mechanisms of schizophrenia, there has been a longstanding tradition to cluster symptoms into domains of psychopathology (411). These signs and symptoms include distortions of thinking and perception, loss of drive (i.e., avolition), cognitive impairments, difficulties in communication, and affective abnormalities (201). While the exact groupings of these signs and symptoms is not entirely certain, empirical studies routinely distinguish between positive, negative, cognitive, disorganization, and mood symptoms (201, 210). While some of these descriptors are intuitive, the positive-negative distinction is less so.

The positive versus negative symptom dichotomy has its origin in the work of the neurologist John Russell Reynolds who used this terminology for positive and negative neurological symptoms to reflect an excess or negation of "vital properties" (e.g., sensation, muscle contractions), respectively (412, 413). For example, positive symptoms included abnormally "superimposed" behaviours such as clonic jerks, whereas negative symptoms included paralysis (412). It was John Hughlings Jackson who developed these ideas further and brought them into the realm of psychiatry, suggesting that negative symptoms reflected a loss of normal function and the dissolution of higher-order systems. When these high-order systems became defective, which he saw as a primary defect, it would result in loss of inhibition and thus release of lower systems; it is this excess activity that he viewed as a positive symptom (413-416). Notably, Jackson, as well others building on his work, viewed negative symptoms as the primary deficit, and positive symptoms were merely consequences (413, 415-417). Applied to behaviour and thought, as is the case in schizophrenia, positive symptoms connote exaggerations in normal functioning (e.g., hallucinations), while negative symptoms connote reductions in normal functions (e.g., loss of drive).

The positive symptoms of schizophrenia, that is psychosis, reflect a break from reality, and specific symptoms include delusions and hallucinations. It is the onset of these symptoms that marks the formal onset of the disorder, and through the course of illness these symptoms can persist and remit to varying degrees. Symptoms related to disorganization involve difficulties in thinking and communication, as well as irregular behaviour. In the realm of thought, these symptoms are sometimes referred to as symptoms of "formal thought disorder," and involve
fragmentations in the logical, progressive, and goal-directed nature of the normal thought process, usually manifesting as incomprehensible speech (418). Disorganized behaviour manifests as inappropriate or incongruous display of affect or inappropriate attire (201). Notably, there are ample inconsistencies in the literature as to what constitutes positive symptoms and/or psychosis and these terms sometimes include both positive symptoms (i.e., delusions and hallucinations) and disorganization, whereas at other times these two are considered distinct (419-428). Adding to the confusion, disorganization symptoms have sometimes and inconsistently been referred to as cognitive symptoms (411, 429-431).

The negative symptoms of schizophrenia will be covered in greater detail in the subsequent sections of this chapter. Briefly, these involve symptoms related to blunting or loss of a range of affective and conative (i.e., motivational) functions, such as affective experience and expression, motivation, hedonic capacity, and speech output (201). Cognitive impairments occur in the context of mental processes underlying information processing (e.g., acquisition and storage of knowledge), and patients with schizophrenia are found to be significantly impaired in their performance on standard cognitive tests (432-438). This deficit seems to reflect, at least in terms of what is detectable using current methods, a generalized cognitive deficit (i.e., an impairment across all cognitive subdomains) (439-441); patients with schizophrenia as a group perform worse than healthy controls on all standard cognitive tests, which is in contrast to notions of specific deficits where patients would demonstrate impairments in some domains of cognition, but relatively preserved functioning in others.

Mood symptoms, including both depressed mood and mania, while obviously more prominent in affective psychotic disorders, also characterize a subset of patients with schizophrenia and, of course, patients with schizoaffective disorder (51, 442-446). Anxiety symptoms are also present in many individuals with schizophrenia (447, 448). Beyond the presence of symptoms, patients with schizophrenia have a high rate of psychiatric co-morbidity, with a significant minority presenting with co-morbid panic disorder or obsessive-compulsive disorder, and almost half having a lifetime diagnosis of a substance use disorder (444).

One of the most striking features of schizophrenia is that many patients lack insight into their illness (449, 450). Lack of insight in psychotic patients may reflect patients' belief that they are, in fact not ill, their tendency to misattribute symptoms to other causes, and/or their denial of
treatment (450-452). Notably, investigations into patients' insight into illness have thus far focused almost exclusively on insight into psychotic symptoms associated with the illness, and few studies have examined insight into the negative symptoms and functional deficits experienced by patients. In one older study, patients with schizophrenia were shown vignettes describing various symptoms associated with the illness; they did not endorse negative symptoms as being associated with the illness, and significantly underreported their negative symptom burden (453).

1.2 Negative Symptoms of Schizophrenia

Negative symptoms were acknowledged by both Kraepelin and Bleuler, and each even considered these symptoms as central to the phenomenology of the illness (454); however, they did not refer to these symptoms as "negative." Wing and colleagues in their investigation of institutionalized patients contrasted florid or productive symptoms (i.e., positive symptoms) from symptoms related to a poverty syndrome (i.e., negative symptoms) (455); however, they too did not explicitly adopt the positive-negative terminology. The categorization of positive and negative symptoms in schizophrenia was championed by Strauss, Carpenter, and Bartko in 1974, based on the work of several psychopathologists and the neurological ideas of John Hughlings Jackson (456); notably, these authors based their classification on symptoms that they considered discriminating (33), and to this end, proposed a third category of interpersonal relationship deficits (456). This latter domain may have later evolved into the negative symptom category as the symptom of asociality, highlighting the fluidity of the negative symptom construct and the individual symptoms that fall under its definition.

Ensuing work adopted the conceptualization of negative symptoms, and built upon early notions to include more formal definitions (419, 457). Later work embraced this approach as a means to reduce phenotypic heterogeneity related to schizophrenia by subtyping patients (197, 419, 421, 423, 425, 426, 429, 458-460). Classifying patients based on the relative severity of negative versus positive symptoms continues and evolves with several investigations, for example, examining patients with predominant negative symptoms (308, 310, 461-463).
1.2.1 Individual Symptoms

The negative symptom construct has certainly evolved over time. The specific symptoms to be subsumed under this construct has been an open question for some time, a fact highlighted by the different items covered in the various existing negative symptom assessment instruments (454, 460, 464-470). In 2005, a consensus meeting was held to consolidate existing knowledge on the negative symptoms of schizophrenia, and to highlight areas in need for further clarification (471). Emerging from this meeting was consensus as to what specific symptoms are subsumed under the negative symptom construct. These included blunted affect, alogia, asociality, anhedonia, and avolition (i.e., amotivation) (471). Over 20 years earlier, these exact symptoms were formally recognized as negative symptoms within the context of the Scale for the Assessment of Negative Symptoms (SANS) developed by Nancy Andreasen (472). The SANS also included attentional impairment as a negative symptom, as well as an item related to inappropriate affect, but these symptoms are no longer considered negative symptoms per se, again highlighting the fluidity of the negative symptom construct. The re-classification of these symptoms is based on factor analytic studies demonstrating that these symptoms align more closely with other domains of illness such as disorganization than with other negative symptoms (422, 473). Similar to attentional impairments, other symptoms that are theoretically more closely related to classic conceptualizations of neurocognition, such as poor abstract thinking, have been classified as negative symptoms in the context of the Positive and Negative Syndrome Scale (PANSS) developed by Stanley Kay (474). Here, too, factor-analytic studies have shown that these symptoms do not align closely with other negative symptoms (475, 476).

1.2.2 Primary versus Secondary Etiology

The expression of symptoms is typically ascribed to an underlying disease process; however, this is not always the case. For instance, psychoactive substances can induce positive psychotic symptoms in healthy volunteers (477-480), but these transient effects are not ascribed to a disease process but to the experimental substance. As such, it would be naive to assume that all negative symptoms are inherently linked to the underlying disease process of schizophrenia. The distinction must be made between primary (i.e., idiopathic) and secondary (i.e., non-idiopathic) negative symptoms (481-485). Several factors, other than the disease process itself, may
potentially influence the severity of negative symptoms such as drug-induced akinesia (486) and symptoms such as depression and suspiciousness (481, 483), to name a few.

Figure 1-2. Illustration of potential sources of secondary non-idiopathic negative symptoms

This list is not meant to be exhaustive; rather it is intended to simply highlight the many variables that can potentially influence negative symptom assessment. It should also be noted that although primary and secondary negative symptoms are viewed as distinct, they are in fact not mutually exclusive.


Antipsychotic drugs in particular have been identified as a potential source of secondary (i.e., iatrogenic) negative symptoms (487-490). There are several sources contributing to this line of thinking. First, antipsychotic medications block dopamine D₂ receptors (242-244), and in pre-clinical studies this reduction in dopaminergic transmission has been linked to the dampened
ability of an organism to attribute incentive salience and pursue effortful goal-directed action (491-493). Furthermore, antipsychotics are known to induce extrapyramidal symptoms such as akinesia, which can mimic some negative symptoms (486, 494, 495). Furthermore, there is evidence that a single administration of an antipsychotic to healthy volunteers can induce some negative symptoms (496-498), although not consistently (499). There are no studies though linking chronic administration of antipsychotics to the induction or exacerbation of negative symptoms, a dosing regimen akin to real-world practice. Seemingly at odds with the notion that antipsychotics induce negative symptoms are studies that have shown that negative symptoms improve with antipsychotic treatment (270, 271, 500), even in non-psychotic individuals (501), and withdrawal of antipsychotic medications leads to worsening of negative symptom burden in patients with schizophrenia (502-505). A few studies have been conducted to examine the association between dosage of antipsychotic received and severity of negative symptoms broadly defined. These studies have failed to discern a significant relationship between these two variables (484, 506, 507); moreover, several other studies have examined plasma concentrations of antipsychotics, a marker putatively more proximal to the biological activity of these drugs (508), and these too have failed to find a relationship between this variable and severity of negative symptoms (506, 507, 509, 510). Other studies have failed to link higher antipsychotic occupancy of the dopamine D2 receptor with more severe negative symptoms (511-516). Thus, findings from studies conducted so far suggest that treatment with antipsychotic drugs may not necessarily worsen negative symptoms in patients with schizophrenia.

While some (secondary) negative symptoms resolve following treatment (481, 517), these symptoms are often persistent (518). Persistent negative symptoms could represent either primary idiopathic symptoms or secondary non-idiopathic symptoms that do not resolve despite treatment. There exists a subgroup of patients with schizophrenia who experience primary and enduring negative symptoms, and this group of patients have been classified as having the "deficit syndrome" (519). Deficit syndrome patients are hypothesized to represent a discrete subtype of schizophrenia with unique clinical characteristics, risk factors, and pathophysiology (520-523). Negative symptoms that are idiopathic and persistent are termed "deficit symptoms" (519); however, this terminology has been inconsistently adhered to in the literature, and it is commonplace to use the two terms interchangeably.
1.2.3 Assessment

Clinical rating scales are the mainstay of psychiatric measurement. There exist several rating scales that are either focused exclusively on negative symptoms or include individual negative symptoms items (454, 460, 465-470). Perhaps the most comprehensive of these is the SANS (472), which has been considered the most important rating scale for the assessment of negative symptoms, and has historically provided a wealth of information that has informed current notions of the structure of negative symptom psychopathology (471). The original version of the SANS includes 20 symptoms that fall under 5 subdomains (affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attentional impairment), there is also a subjective score for each subdomain, as well as a clinician-rated global impression rating (472). In a subsequent version of the SANS, the subjective items were dropped (524).

The Brief Psychiatric Rating Scale (BPRS) (525) has been used widely as an outcome measure in clinical trials of schizophrenia. This scale includes several items that tap into the negative symptom construct such as blunted affect, emotional withdrawal, and motor retardation. However, it is notable that it does not capture several other negative symptoms such as avolition or anhedonia. The PANSS was developed specifically for schizophrenia, to provide a balanced approach to evaluating positive and negative symptoms, while also measuring "general psychopathology" symptoms (474). The PANSS includes 7 items within the negative symptom subscale (blunted affect, emotional withdrawal, poor rapport, passive-apatheic withdrawal, difficulty in abstract thinking, lack of spontaneity & flow of conversation, and stereotyped thinking) (474); notably though, factor analytic studies have suggested that some of these items may not cohere with other negative symptoms, and further that some items captured within the general psychopathology subscale better align with the negative symptom construct (e.g., motor retardation), hence a negative "factor" is routinely utilized instead of the original negative subscale of the PANSS (429, 430, 526-555). The PANSS and BPRS, along with the Clinical Global Impressions (CGI) scale (556), which does not tap into negative symptoms directly, are probably the most commonly employed outcome measures in trials evaluating the efficacy of treatments for schizophrenia (245, 252). The PANSS, like the BPRS, also fails to adequately capture some negative symptoms such as avolition, at least in the non-social realm, and anhedonia. Despite the PANSS not being as comprehensive as the SANS, summary scores from
both scales indexing the overall severity of negative symptoms are highly inter-correlated, and some authors have even proposed that they are inter-changeable (557, 558).

While the SANS, PANSS, and BPRS are the most widely employed outcome measures evaluating negative symptoms in schizophrenia, several others exist. The Negative Symptom Assessment (NSA) has been used in a number of empirical studies including clinical trials (559). There are several versions of NSA, and the most commonly used version is comprised of 16 items, and includes symptoms such as restricted speech quantity, reduced interests, reduced daily activity and reduced expressive gestures, but does not include items adequately covering anhedonia (560). There are also numerous other clinician-rated instruments that focus on negative symptoms, including the Emotional Blunting Scale (EBS) by Abrams and Taylor (561), the Manchester Scale by Krawiecka and colleagues (562), the Negative Symptom Rating Scale (NSRS) by Iager, Kirch and Wyatt (563), the High Royds Evaluation of Negativity (HEN) by Mortimer and colleagues (564), the World Health Organization (WHO) Psychological Impairments Rating Schedule (WHO/PIRS) by Biehl and colleagues (565), the Behavioural Observation Schedule (BOS) by Atakan and Cooper (566), a negative symptom scale by Lewine, Fogg and Meltzer (567), a different negative symptom scale by Pogue-Geile and Harrow (568), yet another negative symptom scale by Pearson and colleagues (569), the negative symptom subscale of the Inpatient Multidimensional Psychiatric Scale (IMPS-Neg) by Gibbons and colleagues (570), and the Motor-Affective-Social Scale (MASS) by Tremeau and colleagues (571), each of which have varying degrees of overlap in item content (454, 460, 465). More recently, the Brief Negative Symptom Scale (BNSS) (572) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (573) have emerged as novel rating scales for the assessment of schizophrenia, whose development was based on recommendations from the 2005 consensus meeting on negative symptoms (471). Both with 13 items each, these scales cover symptoms related to affective flattening, alogia, asociality, anhedonia, and avolition (i.e., amotivation), albeit the focus of the items differs somewhat (572, 573). There also exists a single item measure of overall burden of negative symptoms embedded within the CGI - Schizophrenia (CGI-SCH) scale, and it is notable that this single item has shown a high inter-correlation with a PANSS negative factor score (574). Such a single item rating of overall burden of negative symptoms has also been adopted in the recent DSM-5 Clinician-rated Dimensions of Psychosis Symptom Severity (DSM-5-SS) scale (17).
Table 1-4. Item composition of clinician-rated negative symptom instruments

<table>
<thead>
<tr>
<th>Clinical rating scale</th>
<th>Items (subscales are underlined, if applicable; and, items are numbered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scale by Wing (575)</td>
<td>Social Withdrawal: 1) Slow; 2) Underactive; 3) Lack of conversation; 4) Social withdrawal; 5) Indifference; 6) Poor personal hygiene; 7) Careless appearance; 12) Poor mealtime behaviour</td>
</tr>
<tr>
<td>BPRS (556)</td>
<td>Anergia: 1) Emotional withdrawal; 2) Motor retardation; 3) Blunted affect; 4) Disorientation</td>
</tr>
<tr>
<td>IMPS-Neg (570)</td>
<td>Apathy: 1) Apathy toward treatment; 2) Apathy toward environment; Retardation: 3) Slow speech; 4) Fixed facial expression; 5) Slow movement 6) Thought blocking; 7) Poverty of speech; Bleulerian/loss of goal: 8) Irrelevant speech; 9) Incoherent speech; 10)Wandering speech; 11) Inappropriate affect</td>
</tr>
<tr>
<td>Manchester Scale (576)</td>
<td>1) Poverty of speech, mute; 2) Flattened incongruous affect; 3) Psychomotor retardation</td>
</tr>
<tr>
<td>EBS (561)</td>
<td>Affect subscale: 1) Absent, shallow, incongruous mood; 2) Constricted affect; 3) Unvarying affect; 4) Unrelated affect; Behaviour: 5) Expressionless face; 6) Unvarying, monotonous voice; 7) Seclusive/withdrawn, avoids social contact; 8) Lacks social gestures; 9) Difficult to excite emotions/unresponsive; 10) Lacks spontaneity; 11) Causeless, silly laughter/silly disposition; 12) Indifferent to surroundings; Thought content: 13) Indifference/lack of affection for family, friends; 14) Indifference/unconcern for own present situation; 15) Indifference/unconcern for own future; 16) Paucity of thought</td>
</tr>
<tr>
<td>SANS (472)</td>
<td>Affective flattening or blunting: 1) Unchanging facial expression; 2) Decreased spontaneous movements; 3) Paucity of expressive gestures; 4)</td>
</tr>
<tr>
<td>Scale by Lewine and colleagues (567)</td>
<td>1) Fatigue; 2) Loss of interest; 3) Loss of sexual interest; 4) Slowed speech; 5) Slowed body movements; 6) Depressed appearance; 7) Inappropriate affect; 8) Blunted affect; 9) Loose associations; 10) Poverty of content; 11) Incoherence</td>
</tr>
<tr>
<td>Scale by Pearlson and colleagues (569)</td>
<td>1) Poverty of speech; 2) Apathy; 3) Poor personal hygiene; 4) Emotional flattening; 5) Absence of friends; 5) Asexuality</td>
</tr>
<tr>
<td>Scale by Pogue-Geile and Harrow (568)</td>
<td><strong>Poverty of speech:</strong> 1) Long lapses before replying; 2) Restriction of quantity; 3) Patient fails to answer; 4) Speech slowed; 5) Blocking; <strong>Flat affect:</strong> 6) Avoids looking at the interviewer; 7) Blank, expressionless face; 8) Reduced emotion shown when emotional material discussed; 9) Apathetic &amp; uninterested; 10) Monotonous voice; 11) Low voice, difficult to hear; <strong>Psychomotor retardation:</strong> 12) Slowed movements; 13) Reduction in voluntary movements</td>
</tr>
<tr>
<td>NSRS (563)</td>
<td><strong>Thought process:</strong> 1) Speech content; 2) Decision/judgment; <strong>Cognition:</strong> 3)</td>
</tr>
<tr>
<td></td>
<td>Memory; 4) Attention; 5) Orientation; Volition/motivation; 6) Grooming; 7) Motivation; 8) Motion; Affect/relatedness; 9) Emotional response; 10) Expressive relatedness</td>
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<tr>
<td><strong>PANSS (474)</strong></td>
<td><strong>Negative subscale:</strong> 1) Blunted affect; 2) Emotional withdrawal; 3) Poor rapport; 4) Passive-apatheetic social withdrawal; 5) Difficulty in abstract thinking; 6) Lack of spontaneity &amp; flow of conversation; 7) Stereotyped thinking</td>
</tr>
<tr>
<td><strong>HEN (564)</strong></td>
<td><strong>Appearance:</strong> 1) Face and hair; 2) Body; 3) Clothes; 4) Global rating of appearance; <strong>Behaviour:</strong> 5) Reduced facial expression; 6) Reduced expressive gestures; 7) Slowness/clumsiness of movement; 8) Global rating of behaviour; <strong>Speech:</strong> 9) Reduced in quantity; 10) Lacks inflection; 11) Slowness/latency of speech; 12) Global rating of speech; <strong>Thought:</strong> 13) Impoverishment of thought; 14) Poor performance of tests of attention/concentration; 15) Global rating of thought; <strong>Affect:</strong> 16) Constricted affect; 17) Emotional withdrawnness; 18) Shallow/coarsened affect; 19) Global rating of affect; <strong>Functioning:</strong> 20) Reduced interests; 21) Social withdrawal; 22) Reduced sexual interest; 23) Work impairment; 24) Global rating of functioning</td>
</tr>
<tr>
<td><strong>BOS (566)</strong></td>
<td><strong>Self-presentation:</strong> 1) Self-presentation; <strong>Activity:</strong> 2) Sleepiness; 3) Attention disorders; 4) Psychic tempo; 5) Initiative; <strong>Display of affect:</strong> 6) Display of quantity of affect; 7) Display of quality of affect; 8) Other disturbances of</td>
</tr>
<tr>
<td>NSA 26-item version (559)</td>
<td>Affect/Emotion: 1) Restricted speech quantity; 2) Monotonous voice; 3) Low voice, difficult to hear; 4) Reduced expressive gestures; 5) Blank, expressionless face; 6) Affect: reduced range; 7) Affect: reduced depth; 8) Emotion: reduced range; 9) Emotion: reduced depth; 10) Poor rapport with interviewer; External environment: 11) Reduced social drive; 12) Reduced sense of purpose; 13) Reduced interests; 14) Reduced daily activity; 15) Little awareness of recent events; Retardation: 16) Long lapses before replies; 17) Speech slowed; 18) Slowed movement; Personal presentation: 19) Impoverished speech content; 20) Mumbled, garbled speech; 21) Poor grooming and hygiene; Thinking: 22) Concrete thinking; 23) Poor memory; Interpersonal interest: 24) Avoids looking at interviewer; 25) Reduced sexual interest; Blocking: 26) Speech blocked</td>
</tr>
<tr>
<td>NSA 30-item version (578)</td>
<td>Difficulties in communicating: 1) Long lapses before replies; 2) Restricted speech quantity; 3) Impoverished speech content; 4) Fails to answer; 5) Speech slowed; 6) Speech blocked; 7) Monotonous voice; 8) Low voice, difficult to hear; 9) Mumbled, garbled speech; 10) Reduced expressive gestures; Lack of emotion/flattened affect: 11) Blank, expressionless face; 12) Emotion: reduced range; 13) Emotion: reduced experience; 14) Affect: reduced range; 15) Affect: reduced use; 16) Affect: reduced perception (visual); 17) Affect: reduced perception (auditory); Social inactivity: 18) Reduced social drive; 19) Poor rapport with interviewer; 20) Avoids looking at interviewer; 21) Reduced sexual interest; Loss of interest/motivation: 22) Poor grooming and hygiene; 23) Reduced sense of purpose; 24) Reduced interest; 25) Reduced daily activity; Cognitive difficulties: 26) Little awareness of recent events; 27) Concrete; 28) Poor memory; 29) Temporal disorientation; Psychomotor retardation: 30) Slowed movements</td>
</tr>
<tr>
<td>NSA 16-item</td>
<td>Communication: 1) Prolonged time to respond; 2) Restricted speech</td>
</tr>
<tr>
<td>Version (560)</td>
<td>Quantity; 3) Impoverished speech content; 4) Inarticulate speech; Emotion/Affect: 5) Emotion: reduced range; 6) Affect: reduced modulation; 7) Affect: reduced display; Social involvement: 8) Reduced social drive; 9) Poor rapport with interviewer; 10) Reduced sexual interest; Motivation: 11) Poor grooming and hygiene; 12) Reduced sense of purpose; 13) Reduced hobbies and interest; 14) Reduced daily activity; Retardation: 15) Reduced expressive gestures; 16) Slow movements</td>
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<tr>
<td>MASS (571)</td>
<td>1) Co-verbal gestures; 2) Spontaneous smiles; 3) Voluntary smiles; 4) Number of questions; 5) Motor activity; 6) Hygiene; 7) Activity/groups; 8) Verbal interactions</td>
</tr>
<tr>
<td>CAINS (573)</td>
<td>Social (motivation &amp; pleasure): 1) Motivation for close family/spouse/partner relationships; 2) Motivation for close friendships &amp; romantic relationships; 3) Frequency of pleasurable social activities - past</td>
</tr>
</tbody>
</table>
week; 4) Frequency of pleasurable social activities - next week; **Work & school (motivation & pleasure):** 5) Motivation for work & school activities; 6) Frequency of expected pleasurable work & school activities - next week; **Recreation (motivation & pleasure):** 7) Motivation for recreational activities; 8) Frequency of pleasurable recreational activities - past week; 9 Frequency of pleasurable recreational activities - next week; **Expression:** 10) Facial expression; 11) Vocal expression; 12) Expressive gestures; 13) Quantity of speech

Table 1-5. Individual symptoms covered by various negative symptom scale

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Affective flattening</th>
<th>Alogia</th>
<th>Amotivation (or apathy)</th>
<th>Anhedonia</th>
<th>Asociality</th>
<th>Cognition</th>
<th>Disorganized speech or behaviour</th>
<th>Motor retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS Anergia Factor</td>
<td>X</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>P</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>IMPS - Neg</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>O</td>
<td>P</td>
<td>O</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Manchester Scale</td>
<td>X</td>
<td>X</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>P</td>
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<tr>
<td>EBS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td>SANS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Scale by Lewine et al.</td>
<td>X</td>
<td>X</td>
<td>P</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td>Scale by</td>
<td>X</td>
<td>X</td>
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<td>Pearlson et al.</td>
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<td>Scale by</td>
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<td>Pogue-Geile and Harrow</td>
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<td>NSRS</td>
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<tr>
<td>PANSS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>O</td>
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<td>Negative Subscale</td>
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<td>NSA-30</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>MASS</td>
<td>X</td>
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<td>CAINS</td>
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<td>X</td>
<td>X</td>
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<td>O</td>
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</tbody>
</table>

Note: X indicates definite inclusion of at least a single item evaluating the negative symptom in question; P indicates possible inclusion or inclusion of items that partially evaluate the negative symptom in question; O indicates a lack of inclusion. This table has been adapted from previous work (454, 460, 465).

The Schedule for the Deficit Syndrome (SDS) is a specialized instrument that was designed to aid in the classification of patients who have primary and enduring negative symptoms (i.e., the
deficit syndrome) (581). The scale covers 6 negative symptoms (restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive), as well as additional items comprising ratings of whether each of these symptoms is primary in nature, and whether it has endured for at least the past year (581). Though this scale includes severity ratings for 6 negative symptoms, it was not designed to be used as a standalone negative symptom severity measure.

Beyond clinician or observer rated instruments, several tools have been constructed to focus on the patient's perspective of their negative symptom burden. The validity of such a self-report methodology has been debated, but in general self-report scales show good convergence with clinician-rated symptoms, and offer the potential to be used as relatively quick screening tools. Examples of self-report negative symptoms scales include the Subjective Experience of Negative Symptoms (SENS) scale (582), a self-report version of the CAINS (583), a self-report measure of the motivation and pleasure subdomain of the CAINS (584), the Positive and Negative Symptoms Questionnaire (PNS-Q) (585), the Physical Anhedonia Scale (PAS) and the Scale for Social Anhedonia (SSA) (586), and more recently the Self-Evaluation of Negative Symptoms (SNS) (587). The Subjective Deficit Syndrome Scale (SDSS), despite its name and use in some studies to evaluate self-reported negative symptoms, is better conceptualized as a broad measure of subjective experiences in schizophrenia, not necessarily linked to negative symptoms (588, 589). In addition, the Subjective Experience of Deficits in Schizophrenia (SEDS) taps into negative symptoms as well as other subjective deficits (e.g., relating to disorganization) (590).

Most of the aforementioned scales have been developed specifically to address negative symptoms, with the first such negative symptoms specific scale appearing in 1978 (561). The evaluation of symptoms that now fall under the negative symptom construct have, however, been the focus of assessment and have been included in various rating scales that both precede and post-date the emergence of negative symptom specific instruments. One of the earlier efforts to systematically evaluate symptoms, including negative symptoms, came from John Wing and Peter Venables, both from the United Kingdom, who created scales to measure behaviour in chronically institutionalized patients (575, 591, 592). For example, one of the scales included items tapping into indifference to one's environment, passive social withdrawal, and slowness of movements (592). Other scales were also developed around the same time to evaluate ward
behaviour (593-595). Later, more systematic instruments to assess psychiatric symptoms, including negative symptoms, were developed (596, 597).

There have also been attempts to evaluate negative symptoms more objectively. Advances in technology and computational power have made this possible. For example, poverty of speech can be evaluated using computerized assessment of speech (598-600). Computerized detection of facial features can also be utilized to evaluate emotional expression and blunting of affect (601, 602). Outside of computerized assessments, electromyography has also been used to detect variation in facial emotion expression (603-606). These offer several advantages over traditional clinical rating scales, including the quantitative continuous nature of their readouts. In addition to these, there also exist efforts to examine symptoms in a more ecologically valid setting. For instance, in one study, during the break of an experimental laboratory session, patients were given the choice between playing a computer game, or they could alternatively sit idle, and the amount of time they engaged in the game was taken as a proxy for the real-world interest, curiosity or motivation (607). In addition, digital motion capture has been employed to evaluate non-verbal communication, such as the use of gestures, among patients with schizophrenia (608, 609). There is also growing interest in using virtual reality technology in schizophrenia (610). A few studies have explored the interactions between patients with schizophrenia and virtual avatars as a means to garner insight into social communication deficits related to asocial behaviour (611-613).

1.2.4 A Distinct Domain of Psychopathology

Psychopathology that is outside the construct can certainly influence negative symptom expression (e.g., secondary negative symptoms), but negative signs and symptoms are not merely the co-expression of these other symptoms; negative symptoms represent a distinct domain of psychopathology in their own right. Several lines of evidence have supported this notion, including a wealth of factor analytic studies that have shown that negative symptoms tap into a latent construct that is different from other symptoms such as positive psychotic symptoms. Since its publication in 1987, several studies have explored the factor structure of the PANSS in patients with schizophrenia, including a range of samples (e.g., first-episode, chronic) and emerging from around the world (e.g., India, Singapore), and each of these investigations has
demonstrated the existence of negative symptoms independent from other schizophrenia symptoms (e.g., positive symptoms, depressive symptoms) (429-431, 526-555). Similar results have been found with the SANS and Scale for the Assessment of Positive Symptoms (SAPS) (614), where negative symptoms form a factor distinct from other symptoms such as disorganization (419-422, 473, 528, 615-632). The independence of negative symptoms from positive psychotic symptoms for example is supported by studies demonstrating differential correlates and course of these different symptom dimensions (423, 427, 458, 633-636).

Negative symptoms are often related to severity of depressive symptoms. This relationship however has been inconsistent and the magnitude of relationship does not suggest that these constructs are redundant, rather that there exists a modest amount of overlap. Determining the precise relationship between these constructs is muddied by the fact that there is overlap in items that are considered negative versus depressive symptoms (495, 637-639). For example, several rating scales that have been developed for evaluating symptoms of depression include items relating to psychomotor retardation, loss of energy, diminished interest, and loss of pleasure (640-644). In fact, several reports have suggested that patients with Major Depressive Disorder (MDD) experience prominent negative symptoms, as defined and evaluated by the SANS (645-648). The Calgary Depression Scale for Schizophrenia (CDSS) is a clinical rating scale designed to assess depression in the context of schizophrenia specifically, and does not include negative symptom items (649, 650). Investigations of the inter-relationship between negative symptoms and depressive symptoms (e.g., depressed mood) using the CDSS have revealed only a small correlation between the two constructs, with several studies reporting non-significant statistics (573, 651-659).

Numerous studies have also documented cross-sectional overlap between negative symptoms and cognitive test performance in patients with schizophrenia. For example, one meta-analysis reported a correlation coefficient of about -0.24 for the relationship between these 2 variables (660), a finding that is consistent with large-scale studies (661, 662). The overlap between these two constructs cannot be ascribed to overlap in "item content" as the measurements and their focus are divergent - negative symptoms being assessed by clinician ratings of behaviour, emotion, and thought, while cognition is evaluated by performance-based tests. However, there is conceptual overlap (663). Negative symptoms have historically been defined as symptoms involving a loss or reduction of normal functioning, while impairments in cognitive functioning
are ascribed to deficits in corresponding neural processes subserving mental operations (e.g., attention), and can therefore also be classified as a reduction in normal functioning. Based on these definitions, impairments in neural processing can be termed both as a negative symptom and a cognitive deficit. This conceptual overlap has even seeped into the measurement literature, with the SANS including 2 items related to attentional impairment and the NSRS including a cognition subscale. Conceptual overlap aside, longitudinal studies have failed to find substantial co-variation between the course of negative symptoms and that of cognitive impairments (663-665).

1.2.5 Subdomains: Deconstructing the Unitary Construct

Various individual negative symptoms have been identified, dating back to the early descriptions by Kraepelin and Bleuler, and through the decades selected negative symptoms have been incorporated into formal rating scales. The definition of negative symptom severity has relied on the "overall" picture of these symptoms; that is, the sum total of the severity of individual negative symptoms. Overall negative symptom severity has been employed as an outcome measure in most studies on the topic since the formalization of negative symptom rating scales in the late 1970's/early 1980's, and through these investigations, the field has appreciated the importance of this domain of schizophrenia psychopathology. Parallel to this work emerged psychometric evaluations of the negative symptom tools including examinations of their internal consistency, reliability, and validity (e.g., convergent validity), as well as investigations into the internal factor structure of negative symptoms. Factor analytic studies have played an instrumental role in advancing our understanding of negative symptoms; contemporary notions of schizophrenia no longer view these symptoms as unitary, but multi-factorial, with most evidence supporting the existence of two distinct, yet inter-related, underlying factors (454, 666, 667). These factors are broadly referred to as expressive deficits, which includes symptoms of affective flattening and alogia (specifically poverty of speech), and a second factor termed motivational deficits (or motivation and pleasure deficits, or experiential deficits, or apathy), and includes symptoms of asociality, avolition (i.e., amotivation), and anhedonia. This two-factor structure of negative symptoms has been replicated across a number of studies including diverse patient populations, and with different negative symptom rating scales.
The two-factor structure has been most widely explored with the SANS, perhaps due to its earlier introduction into the literature compared to other negative symptom specific rating scales or due to its comprehensive coverage of individual symptoms. In exploring the structure of the SANS, several important advances on the nature of negative symptoms have been made. Perhaps chief among these is that not all symptoms included in the SANS cohere with the remaining negative symptom items, and may instead align better with symptoms of disorganization, a finding that is bolstered when the factor structure of the SANS and SAPS is examined together (422, 473); specifically, items within the attentional impairments subscale, the inappropriate affect item, and the poverty of content of speech item are no longer considered negative symptoms, but instead symptoms of disorganization. As such, factor analytic studies that have included these items in their analysis have routinely yielded a three-factor structure, with the third factor reflecting symptoms of disorganization (i.e., a non-negative symptom factor).

### Table 1-6. Summary of studies exploring the factor structure of negative symptoms in schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Clinical rating scale</th>
<th>Factor structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg et al. 1963 (668)</td>
<td>450</td>
<td>IMPS</td>
<td>1) Slowed speech and movements (i.e., poverty of speech); 2) Indifference to environment (i.e., avolition)</td>
</tr>
<tr>
<td>Gibbons et al. 1985 (570)</td>
<td>416</td>
<td>IMPS-Neg</td>
<td>1) Apathy (i.e., avolition); 2) Retardation (i.e., affective flattening, poverty of speech); 3) Bleulerian/loss of goal (i.e., disorganization)</td>
</tr>
<tr>
<td>Alphs et al. 1989 (559)</td>
<td>100</td>
<td>NSA</td>
<td>1) Affect/Emotion; 2) External involvement; 3) Retardation; 4) Personal presentation; 5) Thinking; 6) Interpersonal interest; 7) Blocking</td>
</tr>
<tr>
<td>Keefe et al.</td>
<td>130</td>
<td>SANS</td>
<td>1) Diminished expression (i.e., affective flattening,</td>
</tr>
<tr>
<td>Year</td>
<td>Methodology</td>
<td>Sample Size</td>
<td>Included Measures</td>
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<td>------------------------------------------------------------------------------------</td>
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<tr>
<td>1992 (669)</td>
<td></td>
<td></td>
<td>poverty of speech; 2) Social dysfunction (i.e., avolition, asociality, and anhedonia); 3) Disorganization (i.e., inappropriate affect, poverty of content speech)</td>
</tr>
<tr>
<td>Raskin et al. 1993 (578)</td>
<td></td>
<td>101 NSA</td>
<td>1) Restricted affect/behaviour; 2) Emotion perception deficits; 3) Speech retardation; 4) Poor speech Quantity; 5) Poor grooming/hygiene; 6) Temporal disorientation; 7) Reduced social/sexual interest</td>
</tr>
<tr>
<td>Axelrod et al. 1994 (670)</td>
<td></td>
<td>233 NSA</td>
<td>1) Communication; 2) Emotion/Affect; 3) Social involvement; 4) Motivation; 5) Gross cognition; 6) Retardation</td>
</tr>
<tr>
<td>Minas et al. 1994 (618)</td>
<td></td>
<td>114 SANS and SAPS</td>
<td>2) Negative signs (i.e., affective flattening, poverty of speech); 2) Social dysfunctions (i.e., asociality, avolition, anhedonia)</td>
</tr>
<tr>
<td>Mueser et al. 1994 (671)</td>
<td></td>
<td>207 SANS</td>
<td>1) Affective flattening or blunting (and poverty of speech); 2) Avolition-apathy and Anhedonia-asociality; 3) Alogia and Inattention</td>
</tr>
<tr>
<td>Peralta and Cuesta 1995 (672)</td>
<td></td>
<td>253 SANS</td>
<td>1) Affective flattening; 2) Alogia; 3) Avolition-apathy; 4) Anhedonia-asociality; 5) Attention</td>
</tr>
<tr>
<td>Sayers et al. 1996 (673)</td>
<td></td>
<td>437 SANS</td>
<td>1) Diminished expression (i.e., affective flattening); 2) Inattention-alogia; 3) Social amotivation (i.e., asociality, avolition, anhedonia)</td>
</tr>
<tr>
<td>Toomey et al. 1997 (625)</td>
<td></td>
<td>549 SANS and SAPS</td>
<td>1) Diminished expression (including poverty of speech); 2) Disordered relating (i.e., asociality, anhedonia)</td>
</tr>
<tr>
<td>Peralta and</td>
<td></td>
<td>660 SANS and</td>
<td>1) Poverty of affect/speech (i.e., affective flattening,</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Rating Scale</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cuesta 1999 (674)</td>
<td>SAPS</td>
<td>poverty of speech; 2) Social dysfunction (i.e., asociality, avolition, anhedonia); 3) Attention; 4) Inappropriate Affect</td>
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<tr>
<td>Kelley et al. 1999 (488)</td>
<td>SANS and SAPS</td>
<td>1) Affective flattening (including poverty of speech); 2) Diminished motivation (i.e., asociality, avolition, anhedonia)</td>
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</tr>
<tr>
<td>Emsley et al. 2001 (630)</td>
<td>SANS and SAPS</td>
<td>1) Diminished expression (i.e., affective flattening, poverty of speech, avolition); 2) Disordered relating (i.e., asociality, anhedonia); 3) Though disorder (i.e., inappropriate affect); 4) Bizzare behaviour (i.e., grooming/hygiene)</td>
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<tr>
<td>Malla et al. 2002 (675)</td>
<td>SANS</td>
<td>1) Flat affect/alogia (i.e., affective flattening, poverty of speech, grooming and hygiene); 2) Avolition/anhedonia (i.e., asociality, avolition, anhedonia); 3) Attention (i.e., inappropriate affect, poverty of content of speech, social inattentiveness)</td>
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<tr>
<td>Kimhy et al. 2006 (676)</td>
<td>SDS</td>
<td>1) Avolition (i.e., curbing of interests, diminished sense of purpose, diminished social drive); 2) Emotional expression (i.e., restricted affect, diminished emotional range, poverty of speech)</td>
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<tr>
<td>Nakaya and Ohmori 2008 (677)</td>
<td>SDS</td>
<td>1) Avolition (i.e., diminished sense of purpose, diminished social drive, curbing of interests); 2) Poor emotional expression (i.e., diminished emotional range, restricted affect, poverty of speech)</td>
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<tr>
<td>Trémeau et al. 2008 (571)</td>
<td>MASS</td>
<td>1) Motor-affective (i.e., affective flattening); 2) Motor-social (i.e., avolition, asociality)</td>
<td></td>
</tr>
<tr>
<td>Rabany et al. 240 SANS</td>
<td>SANS</td>
<td>1) Affective flattening; 2) Avolition-apathy; 3)</td>
<td></td>
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<tr>
<td>Year (Reference)</td>
<td>Methodology</td>
<td>Dimension 1</td>
<td>Dimension 2</td>
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<tr>
<td>2011 (659)</td>
<td></td>
<td>Alogia; 4) Anhedonia-asociality</td>
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<tr>
<td>Kirkpatrick et al. 2011 (572)</td>
<td>20 BNSS</td>
<td>1) Anhedonia/Avolition/Asociality; 2) Emotional expressivity (i.e., affective flattening, poverty of speech)</td>
<td></td>
</tr>
<tr>
<td>Horan et al. 2011 (580)</td>
<td>281 CAINS</td>
<td>1) Experiential impairments (i.e., asociality, avolition, anhedonia); 2) Expressive impairments (i.e., affective flattening, poverty of speech)</td>
<td></td>
</tr>
<tr>
<td>Strauss et al. 2012 (678)</td>
<td>146 BNSS</td>
<td>1) Motivation and pleasure (i.e., asociality, avolition, anhedonia); 2) Emotional expressivity (i.e., affective flattening, poverty of speech, lack of distress)</td>
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</tr>
<tr>
<td>Strauss et al. 2013 (679)</td>
<td>199 SANS</td>
<td>1) Diminished expression (i.e., affective flattening, alogia); 2) Avolition-apathy (i.e., asociality, avolition, anhedonia)</td>
<td></td>
</tr>
<tr>
<td>Strauss et al. 2013 (679)</td>
<td>169 SDS</td>
<td>1) Avolition-apathy (i.e., curbing of interests, diminished sense of purpose, diminished social drive); 2) Diminished expression (i.e., restricted affect, diminished emotional range, poverty of speech)</td>
<td></td>
</tr>
<tr>
<td>Levine and Leucht 2013 (680)</td>
<td>487 SANS</td>
<td>1) Affective flattening (and poverty of speech); 2) Asociality (and avolition and anhedonia); 3) Alogia-inattentiveness (and inappropriate affect)</td>
<td></td>
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<tr>
<td>Galderisi et al. 2013 (681)</td>
<td>77 SDS</td>
<td>1) Poor emotional expression (i.e., restricted affect, diminished emotional range, poverty of speech); 2) Avolition (i.e., curbing of interests, diminished sense of purpose, diminished social drive)</td>
<td></td>
</tr>
<tr>
<td>Lyne et al. 2013 (682)</td>
<td>191 SANS</td>
<td>1) Expressivity (i.e., affective flattening, poverty of speech); 2) Experiential (i.e., asociality, avolition, anhedonia); 3) Alogia/Inattention</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Scale</td>
<td>Expressive Deficits</td>
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<tr>
<td>Liemburg et al. 2013</td>
<td>664</td>
<td>PANSS</td>
<td>1) Expressive deficits (i.e., flat affect, motor retardation, poverty of speech, poor rapport, mannerisms, &quot;avolition&quot;); 2) Social amotivation (i.e., passive apathetic withdrawal, emotional withdrawal, active social avoidance)</td>
</tr>
<tr>
<td>Kring et al. 2013</td>
<td>162</td>
<td>CAINS</td>
<td>1) Expression (i.e., affective flattening, poverty of speech); 2) Motivation/pleasure (i.e., asociality, avolition, anhedonia)</td>
</tr>
<tr>
<td>Engel et al. 2014</td>
<td>53</td>
<td>CAINS</td>
<td>1) Expression (i.e., affective flattening, poverty of speech); 2) Motivation/pleasure (i.e., asociality, avolition, anhedonia)</td>
</tr>
<tr>
<td>Fervaha et al. 2014</td>
<td>754</td>
<td>PANSS</td>
<td>1) Diminished expression (i.e., blunted affect, motor retardation, poverty of speech, poor rapport); 2) Amotivation (i.e., passive apathetic withdrawal, emotional withdrawal, active social avoidance)</td>
</tr>
<tr>
<td>Mucci et al. 2015</td>
<td>912</td>
<td>BNSS</td>
<td>1) Avolition (i.e., asociality, avolition, anhedonia); 2) Poor emotional expression (i.e., affective flattening, poverty of speech)</td>
</tr>
<tr>
<td>Garcia-Portilla et al.</td>
<td>20</td>
<td>BNSS</td>
<td>1) External world (i.e., anhedonia, asociality); 2) Inner world (i.e., avolition, blunted affect); 3) Alogia (i.e., poverty of speech)</td>
</tr>
<tr>
<td>Valienete-Gomez et al.</td>
<td>100</td>
<td>CAINS</td>
<td>1) Motivation/pleasure (i.e., asociality, avolition, anhedonia); 2) Expression (i.e., affective flattening, poverty of speech)</td>
</tr>
<tr>
<td>Chan et al. 2015</td>
<td>68</td>
<td>CAINS</td>
<td>1) Expression (i.e., affective flattening, poverty of speech); 2) Motivation/pleasure (i.e., asociality, avolition, anhedonia)</td>
</tr>
</tbody>
</table>
While each individual negative symptom factor analytic study does not support the two-factor structure, or does not agree on which specific symptoms should be classified into one factor versus another, there is clear evidence that the underlying structure of negative symptoms is complex and multi-factorial; each study has supported the notion of a multi-factorial view of negative symptoms over the unitary factor concept (666). At any rate, across all investigations, the two-factor structure accrues the most evidence. Support for two discrete factor characterizing negative symptoms comes from numerous studies showing that the two facets have differential correlates, despite being inter-related (488, 573, 580, 673, 675, 677, 679, 683-685, 688-691).

In recognition of the distinction between the two subdomains, as well as the growing recognition of the importance of the motivational deficits subdomain, several standalone instruments have been used to evaluate this subdomain in patients with schizophrenia. For example, Marin's Apathy Evaluation Scale (AES) (692), which was originally developed for patients with neurological disorders, has shown adequate psychometric properties in patients with schizophrenia (693). This scale covers symptoms of avolition, anhedonia and asociality, but assesses these symptoms from a subjective standpoint in addition to behavioural output. The Lille Apathy Rating Scale (LARS) has also been used in schizophrenia, and has been shown to have adequate psychometric properties (694).
1.2.6 Neurobiology

Insights into the neurobiological correlates of negative symptoms have largely been based on neuroimaging findings. Early findings of a neurobiological substrate for negative symptoms came from investigations employing CT in the 1980's, the standard for that period. One of the earlier reports suggested a possible link between ventricular enlargement and negative symptoms, though the reported finding was not statistically significant (695); notably, other prior investigations also failed to find a significant relationship between ventricular enlargement and negative symptoms, but did report similar non-significant trends, and in addition found a relationship between these CT findings and other markers of poor outcome (340, 696).

Subsequent investigations have not been consistent with respect to this finding, with results mixed (458, 697-703). Nonetheless, these investigations set the stage for the notion that negative symptoms are linked to structural brain changes; hypotheses even emerged suggesting there exists a subgroup of schizophrenia patients characterized by prominent negative symptoms, poor prognosis, and neural degeneration (457, 704).

The search for neuroanatomical correlates of negative symptoms continued with the use of MRI as an investigative tool. An early structural MRI study found a relationship between macroscopic whole-brain MRI measures and severity of negative symptoms, but failed to discern a specific relationship between symptoms and frontal lobe volume in particular (705). A subsequent study did, however, find a relationship between negative symptoms and lower prefrontal volumes (706). This is a particular relevant finding given the resemblance (i.e., overlap) between the negative symptoms of schizophrenia and behavioural traits associated with frontal lobe damage (e.g., apathy) (707-711). There is also evidence that among patients with schizophrenia, apathy in particular is related to lower frontal lobe volumes (712). The relationship of negative symptoms to frontal lobe morphology has also been extended to subregions within the frontal lobe, including the orbitofrontal cortex (OFC) and medial prefrontal cortex (MPFC) (713-716).

Evidence for negative symptoms being linked to prefrontal abnormalities also comes from studies demonstrating an association between these symptoms and hypofunctioning of this region (717-728), as well as evidence showing that as negative symptoms improve there are concurrent increases in frontal lobe activity (729). However, contradictory findings have also
been reported, with some studies failing to replicate the relationship between frontal lobe volume and negative symptom burden (730-733).

Beyond the frontal lobe, negative symptom severity has also been associated with neuroanatomical variation within the temporal cortex (722, 730, 734-739) including the fusiform gyrus (740) and hippocampus (741), corpus callosum (736, 742), ACC (736, 743), and thalamus (744). This suggests that negative symptoms are associated with a distributed network of neuroanatomical alterations, a contention that has recently been shown empirically (745). Notably, apathy in particular has been associated with neuroanatomical alterations in both the OFC and ACC (746). Along these lines, negative symptom burden has also been associated with white matter tract dysconnectivity (747-755), but, as with most neuroimaging findings in schizophrenia, contradictory evidence also exists (756). Furthermore, several studies have demonstrated that negative symptom burden serves as a marker for greater progressive brain volume alterations (388, 389, 757, 758).

A number of fMRI studies have also investigated the potential relationships between functional activity within the brain and negative symptoms. Functioning within the prefrontal cortex (PFC), specifically the ventromedial PFC (VMPFC), and the ventral striatum seem to be related to the relative burden of negative symptoms (759). Findings of disrupted ventral striatal activity are usually seen in the context of reward processing tasks (760). Notably, ventral striatal hypofunction in the context of anticipating a future reward (i.e., reward processing) has been linked to motivational deficits in particular (761). Taken together, these findings should be considered important advances as they provide a biologically plausible mechanism underlying negative symptom expression (i.e., that the neural circuitry underlying reward processing is abnormal in patients with schizophrenia and related to negative symptoms). Altogether, findings to date provide support for the notion that fronto-striatal circuitry, including both structure and function, is related to negative symptoms.

In terms of neurochemistry, negative symptoms have been hypothesized to be related to low levels of dopamine in the PFC (320). This hypothesis has been bolstered by empirical evidence just recently, although the results were mixed; patients with schizophrenia demonstrated lower dopamine release following an amphetamine challenge but this was not related to negative symptom psychopathology (762). There is evidence of low levels of endogenous dopamine
within the ventral striatum being associated with greater negative symptoms, and apathy in particular (763). Striatal hypodopaminergia being linked to apathy has ample biological plausibility, and is supported by numerous pre-clinical studies (493). There are even hypotheses put forth that, based on the presence and course of negative symptoms, schizophrenia is related to a fundamental hypodopaminergic state (764).

1.2.7 Prognostic Value and Impact on Outcome

Negative symptoms have long been considered either markers of poor prognosis or determinants of said poor outcome. Little work has been done to conclusively resolve whether negative symptoms serve as a marker or determinant of outcome, but nonetheless studies have conclusively shown that these symptoms are in fact linked to outcome in some manner. The mechanisms underlying this link however are yet to be elucidated, though some models have been hypothesized. For example, negative symptoms, intrinsic to the disorder, include symptoms of primary avolition and anhedonia (i.e., reductions in internal drive, goal-directed activity, and pleasure-seeking behaviour), and this idiopathic loss of drive may undermine patients' ability to effectively function in the community, including work and social activities. However, it has also been proposed that this association reflects the opposite, specifically that negative symptoms are the consequence of concurrent poor functioning (568, 765). These points aside, negative symptoms are clearly associated with measures of functional outcome among patients with schizophrenia.

The importance of negative symptoms in terms of the prognostic value was acknowledged since these symptoms were consolidated and distinguished from positive symptoms by Strauss, Carpenter, and Bartko in 1974 (456). These authors also empirically demonstrated the association between negative (or "defect" symptoms as they are called sometimes) and outcome (766). Following this, ideas about distinct subtypes of schizophrenia emerged in 1980, with one subtype being characterized by prominent negative symptoms and poor outcome (457). Ensuing work, including numerous investigations with a range of patients at varying stages of illness, has confirmed an association between negative symptoms and measures of functional outcome, including vocational functional, social functioning, and engagement in recreational activities (collectively termed "community" or "real-world" functioning) (178, 427, 458, 485, 636, 685,
These studies have come from around the world, including investigations from Canada, and have included both cross-sectional and longitudinal studies with various lengths of follow-up, and have included a variety of different definitions and tools for the assessment of negative symptoms and functional outcome. Despite this heterogeneity, it is remarkable that these studies have consistently shown a relationship between negative symptoms on the one hand, and functional outcome on the other. Moving beyond an association between variables, there is also evidence that longitudinal change in negative symptoms is associated with changes in functional status (813, 851, 857-859). Together, these cross-sectional and longitudinal analyses support the notion that negative symptom burden is associated with poorer functional outcomes in patients with schizophrenia. A meta-analysis involving over 2,000 patients noted that the zero-order correlation between these variables is of a moderate magnitude (i.e., Pearson's correlation coefficient, r = -0.42) (660). Importantly, there is also evidence that primary negative symptoms are associated with poorer functioning, even after controlling for other factors (485). Beyond the impact of negative symptoms on outcome, the role of other factors, acting independently or through interactions, remains to be established.

Other predictors of functional outcome have also been identified. Perhaps the most consistent other predictor of outcome in schizophrenia is cognitive dysfunction (860-864). This is interesting for several reasons, one of them being the identified relationship between negative symptom burden and degree of cognitive impairment (660-662). To this end, it has been suggested that negative symptoms may, at least partly, mediate the relationship between cognition and functioning (660, 813, 839, 865-867). Beyond cognition, several studies have shown that negative symptom burden contributes to the prediction of functional outcome over and above the contribution made by cognition (817, 868-871).

In recognition of the distinct subdomains of negative symptoms (i.e., motivational deficits and expressive deficits), attention has turned to isolate the role of these discrete domains in determining functional outcome. The importance of the motivational deficits, as opposed to expressive deficits, in predicting functioning has been supported in the literature as the key driver of the relationship between negative symptoms and functioning. This relationship seems intuitive as it links experiential deficits (e.g., impairments in drive) with real-world consequences of said deficits. At any rate, the relationship has also been supported empirically. Perhaps the first suggestion of a differential relationship between negative symptom subdomains and
functioning came from a factor analytic study that explored the relationship between negative symptom factors and functional status (673); this study found a significant relationship between motivational deficits as assessed by the SANS, and functioning across a range of domains. Other studies have also found a relationship between amotivation assessed using the SANS and functioning (793, 839, 872, 873). It is noteworthy that the SANS may not be the ideal tool to evaluate motivational deficits in the context of investigations predicting functioning, as items on the SANS conflate motivation and functioning by indexing behavioural output exclusively. Nonetheless, other investigations using different instruments have as well demonstrated a robust relationship between motivational deficits and functional outcome (607, 685, 779, 805, 845, 850, 865-869, 872, 874-880).

These studies provide robust evidence that negative symptoms are associated with functional outcomes among individuals with schizophrenia. Within the broad negative symptom construct, evidence supports motivational deficits as the key predictors. The predicative value of motivational deficits is independent of other domains of psychopathology, and holds even after others factors are controlled for. That is, motivational deficits hold predictive value for the determination of functioning over and above the role of other symptoms and factors such as cognitive impairments. Taken together, evidence to date has highlighted the functional significance of motivational deficits, and underscored these deficits as an unmet need for individuals with schizophrenia.

1.3 Reward Processing and Effort Computation Deficits in Schizophrenia

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Over the past 2-3 decades, there has been a renaissance and resurgence of interest into understanding the negative symptoms of schizophrenia. This has included countless investigations of reward processing and other mental processes that may underlie these symptoms. Building on the wealth of knowledge gained in the cognitive and affective neuroscience fields, researchers studying schizophrenia have begun to appreciate the intricacies and complexity of the human motivational system. Motivation is increasingly embraced as a multi-faceted construct, with several constituent subprocesses. Among these are processes related to the identification of a goal, the evaluation of the hedonic consequences, and the potential costs associated with pursuing action. Motivational deficits can theoretically manifest following impairments in any one of these computational processes. In recognition of the multi-faceted motivational system, and to explore its implications for furthering our understanding of motivational deficits in schizophrenia, several reviews have been written to explore these topics in greater detail (881-890). The discussion of the motivational system, with particular emphasis on the evaluation and neurobiology underlying effort cost computations in schizophrenia, is further detailed in this section.

1.3.1 Assessment of Amotivation in Schizophrenia

1.3.1.1 Clinical Assessment of Negative Symptoms and Amotivation

The previous section highlighted the many negative symptom assessment instruments that exist. Of note, none of these instruments were primarily developed to assess amotivation in schizophrenia; rather they include specific items that tap into the construct. For example, the SANS has two items within the avolition/apathy subdomain: (1) impersistence at work or school; and (2) physical anergia. These items are rated on a six-point ordinal scale based largely on frequency of reported activity. The SANS also includes an anhedonia/asociality subdomain that includes four items that are rated based partially on patients' recall of their experience of pleasure during recreational and interpersonal activities. Amotivation scores can be inferred from these two subdomains, as suggested by factor analytic studies noted in the previous section.

While most of the scales employed to assess negative symptoms in schizophrenia, with the exception of the BPRS, have been developed specifically for schizophrenia, other instruments not specifically designed for schizophrenia have been employed to measure amotivation. Most
notably, Marin's Apathy Evaluation Scale (AES) (692), which was originally developed for patients with neurological insults, has shown adequate psychometric properties in individuals with schizophrenia (693). This dimensional scale specifically assesses amotivation by reviewing patients’ behaviours (example item: "S/He gets things done during the day") as well as internal motives (example item: "Seeing a job through to the end is important to him/her"). This instrument seems to demonstrate superior psychometric properties over the SANS/PANSS in specifically assessing amotivation. This is likely due to its inclusion of multiple items compared to the two items included in the SANS, as well as its inclusion of subjective experiences over the reliance on overt behaviour. This scale has been used across a number of studies in patients with schizophrenia, and has consistently demonstrated a prominent role of amotivation in predicting functional outcomes (607, 850, 875, 876, 891).

1.3.1.2 Laboratory-based Assessments of Goal-Directed Behaviour in Schizophrenia

There have been efforts at quantifying goal-directed behaviour more objectively than what is possible through patient self-report. One study quantified the amount of self-initiated purposeful behaviours in an inpatient sample of patients with schizophrenia, and found that observable self-initiated behaviours correlated with amotivation as measured clinically using the SANS (892). Another study equipped outpatients with actigraphic monitors to record motor activity, and found that level of activity was inversely related to SANS amotivation scores (893). Other actigraphy studies have reported similar findings (894-896). It should be noted, though, that measures of actigraphy are quite non-specific in that they assess movements of all types, including passive movements. In another study, inpatients with schizophrenia were monitored for exploratory behaviour while in a novel test room, which is analogous to the pre-clinical open-field paradigm (897), and found no difference in exploratory behaviour in patients versus healthy controls (898, 899). Interestingly, this study found that the pattern of movement for patients was less predictable than that of healthy controls and further that there were no differences in the number of interactions with objects; it is of note that this study tested acutely ill patients rather than stable outpatients. In another such study, inpatients with schizophrenia were found to walk more than healthy controls and also spent more time near objects, which was related to severity of psychotic symptoms (900).
One instrumental study used an experimental paradigm to assess patients' self-reported ratings of pleasure/arousal to images of varying affective valence, as well as the amount of effort exerted to seek or avoid future exposure to these images (901, 902). Findings indicated that patients demonstrated deficits in coupling behaviour and ratings relative to healthy volunteers; that is, patients had similar in-the-moment pleasure/arousal ratings in response to the images, but failed to exert effort to seek/avoid these images in the future (902). Interestingly, their measure of effort did not correspond to clinical SANS ratings. This is quite intriguing as it suggests that subjective clinical ratings and objective laboratory measurements of effort or motivation are not necessarily redundant, and by extension may be neurobiologically dissociable. Along similar lines, another study assessed patients’ response to emotional evocative pictures, and also their self-reported motivation to view the pictures again (903). Researchers found that patients did not differ from healthy controls in terms of in-the-moment pleasure and self-reported motivation; however, unlike healthy controls, patients with schizophrenia self-reported motivation was uncoupled from their hedonic responses. Taken together, these two studies suggest a disconnect between motivation and affective response or pleasure reaction among individuals with schizophrenia, possibly impacting volition (902, 903). In addition, a recent study employing an objective paradigm to assess effort-based decision making in patients with schizophrenia found that patients were less willing to expend effort for larger monetary rewards than healthy controls (904). The findings of this important study are discussed in greater detail below.

1.3.2 Pre-Clinical Assessment of Effort and Motivation

1.3.2.1 Progressive Ratio Paradigm

The progressive ratio (PR) paradigm is widely used in animal studies to assess motivation or willingness to work for reward. It involves an effortful response (e.g. pressing a lever) to obtain a reward (e.g. food pellets) (905); however, the number of operant responses needed to receive a reward progressively increases following each reward delivery. For example, in an exponential paradigm, reward would be delivered after 2, then 4, 8, 16, etc., responses. In short, attaining more reward requires progressively greater effort expenditure. The key outcome variable is the number of responses before the animal stops responding and this metric, termed the break-point, is considered a proxy for an animal's motivation for a given reward. One daily life activity where
such processes may operate can be seen in the case of an unemployed individual seeking work by investing effort into developing a résumé, seeking out work opportunities and/or completing interviews. In this scenario, one can quickly appreciate that different individuals will invest different amounts of effort in pursuit of the goal of attaining employment, which is analogous to the pre-clinical metric of a break-point.

### 1.3.2.2 Effort-based Decision Making Paradigm

Another paradigm often used in pre-clinical studies of motivation employs multiple rewards, offering the animal a choice (Figure 1-3) (906, 907). One reward is either more valuable (e.g. milk over stock chow) or will be greater in quantity. However, in order to obtain the greater reward the animal must also expend a greater amount of effort (e.g. climbing a wall). Hence, the animal must choose to either expend effort for a greater reward (HE/HR) or expend less effort for a lower reward (LE/LR). The number of HE/HR choices an animal makes is taken as a proxy of their willingness to expend effort or their motivation for that reward. Along the lines of the previous ecological example given, one everyday situation where this paradigm might operate is in situations where individuals decide between working hard to create an elegant résumé or simply just ‘getting it done’. Another set of examples relevant to patients with schizophrenia are decisions to expend effort to shower, change clothes, complete chores, pursue relationships or engage in passive activities such as lying in bed. We posit that symptoms of amotivation may, at least in part, be explained by impairments in effort cost computations. Specifically, we posit that patients with schizophrenia overestimate effort costs or discount reward value by effort at a steeper rate than healthy controls, and that such computational impairments surface clinically as amotivation/apathy.
Illustration of a T-Maze version of an effort-based decision making task. Animals begin at the bottom of the T-Maze (Start) and decide whether to turn right and expend effort for a large reward or turn left and expend less effort for a smaller reward. Healthy rats tend to prefer the high effort/high reward option (i.e. deciding to turn right rather than left) (908).

This effort-based decision making paradigm has advantages over the PR task, as it can partially disentangle motivational processes from non-specific motor responding. Specifically, the relative number of decisions to engage in HE/HR trials can be quantified, rather than the total number of responses, which might be more susceptible to non-specific motor changes. This is particularly important in studies employing some sort of manipulation (e.g. pharmacological challenges with agents known to affect locomotion), because reductions in motor activity have the potential to be
incorrectly viewed as reductions in willingness to expend effort. Such a distinction between
decision making and operant responding, could for example be disentangled by having subjects
make decisions that are carried out in the future or where only a subset of decision are actually
carried out. Temporal separation of choice and action has been successfully implemented in
some studies already (909, 910).

It should be noted that there is no single version of this effort-based decision making paradigm
that is optimally suited to proxy effort cost computations (in schizophrenia). The general
paradigm can be manipulated and tailored. For example, the type of reward in the two conditions
can be primary, secondary, similar or dissimilar in both conditions; effort costs could be in the
physical or mental domains; temporal presentation of reward could be manipulated to include
situations of explorative or foraging behaviour; the probability of reward receipt could be varied;
reward valence could vary from gains to potential losses. Future studies should attempt to
employ multiple versions of this paradigm in order to assess the robustness of any potential
findings involving effort cost computations.

1.3.3 The Multi-Faceted Nature of Effort and Motivation

1.3.3.1 Effort in the Context of the Broader Reward Processing
Framework

For simplicity, we have thus far referred to effort as a singular construct. However, numerous
processes are involved in the evaluation of a reward, as well as determination to expend effort
and the subsequent action plan - these processes are illustrated in Figure 1-4. It is beyond the
scope of this present article to review fully the components and neural underpinnings of value
guided choice as these have been reviewed elsewhere (911-926). For the purpose of this review,
we are primarily interested in the effort cost computation that occurs while evaluating stimuli
and deciding whether, and to what degree, effort should be expended in pursuit of said stimuli -
this computation occurs along with value-based computations and immediately before a motor
action plan is formed. Although, we are primarily interested in effort cost computations and their
neural substrates, it should be noted that such computations are deeply confounded with value
computations/representations. That is, effort costs are only computed in the face of potential
rewards. Hence, it may be that what we are considering effort cost computations are in fact
utility computations or cost-benefit integrations, and that the neural substrates we outline actually compute an effort discounting factor that is applied to value signals processed elsewhere. Whatever the case may be, the neural substrates outlined clearly subserve some derivative of the effort cost signal either as a pure effort cost computation or as a (effort discounted) utility computation. There is in fact some evidence for the latter (927-930).

Figure 1-4. Hypothetical components of the motivational process underlying goal-directed approach behaviour

The process begins with sensory information to the organism including odor, shape, colour, etc. of a cue. This information is then used to predict the reward that is to follow based on prior learning and expectancy. These potential rewards are then converted to common neural currency
by integrated all available information. Intrinsic in the valuation of reward is the organism’s internal motivational state (e.g. hungry, anergic). After the reward information has been computed, the response cost is evaluated (e.g. the amount of effort required to obtain the reward). After this information has been computed, the organism constructs an action plan to either expend effort to obtain reward or engage in another behaviour. This action plan is then translated to observable behaviour. Of note, only the sensory information and overt behaviour can be observed behaviourally. Following the behaviour and its resultant outcome, the properties of the sensory information may be modulated. For example, after obtaining a reward it may seem more or less palatable. This hypothetical process was adapted from previous work (882, 914, 931).

Studies aimed at clarifying the neurobiology of effort cost computations should control for other confounds affecting the various other computations required both before and after said effort computation. Some examples of confounding variables that should be controlled for are motoric ability (i.e. psychomotor slowing), subjective valuation of reward, and propensity for errors or negative outcomes, to name a few. For example, if a reduction in break-point is seen on a PR task after giving drug X, in order to make inferences about effort computations, we must be sure that drug X does not affect the palatability of the reward or the organism’s overall motoric ability. Otherwise, we risk misconstruing decreases in operant responding as decreases in "motivation." It should be noted that the relationship between these processes is not unidirectional; rather, processing during one step may affect any subsequent or previous step, thereby causing continual updating. It has been found, for example, that an animal’s decision to expend effort will affect palatability (i.e. reward value) during reward receipt (932), as well as affecting reward preference (933-935). Moreover, in humans, selection of a reward among competing choices, may alter the neural representation of the expected hedonic value associated with that reward (936).
1.3.3.2 Research on Effort and Motivation

Although the present article focuses on translational evaluation of effort and its underlying neurobiology, other fields not thoroughly discussed here have undoubtedly advanced our understanding of effort and motivation. This work may assist in informing future research on the neurobiology of effort costs by, for example, providing insight into potential behavioural and/or personality variables that would be important to consider (937-950). For example, variables such as trait industriousness, interest, intrinsic motivation, distress intolerance, punishment avoidance, novelty seeking, self-defeatism, perfectionism and impulsivity may influence motivated behaviour either by mediating effort cost computations or through another motivational process. Consideration of such variables should lead to a more comprehensive understanding of effort and motivation in schizophrenia. For example, in studies considering mental effort costs in schizophrenia, it would seem important to consider individual differences in propensity to engage in effortful tasks in general (951). Moreover, borrowing principles from behavioural economics, it may be worthwhile to examine effects of framing on effort-based decisions (952).

1.3.4 Translational Research

1.3.4.1 Pre-Clinical Research

Examining the neurobiology of a behavioural construct involves examining key neuroanatomical structures that are required for that behaviour, as well as how modulation of underlying neurochemistry affects output. For the purpose of brevity, we shall restrict our discussion to studies employing a forced two-choice effort-based decision making paradigm. Of note, though, dopamine functioning seems central to most tasks involving effortful responses (493, 953, 954).

1.3.4.1.1 Neurochemical Basis of Effort

Salamone and colleagues were the first to employ this effort-based decision making task (906). In their initial version, an animal chose to either freely consume chow or press a lever on a set schedule for more preferable food pellets. Importantly, healthy rats strongly preferred to work
for the food pellets suggesting that effort serves as an action cost; however, some animals may actually prefer to expend effort (955-957). The willingness to expend effort observed in healthy rats has been found to be reversed following dopamine depletion focally to the nucleus accumbens (NAc; using haloperidol or 6-hydrdoxydopamine) (906, 907), specifically to the NAc core (958). Follow-up studies indicated that this reduction in decisions to expend effort (i.e. select HE/HR trials) could not be accounted for by motor deficits, simple decision-making impairments or an effect on valuation; animals, when presented with HR and LR options with equally effortful barriers, chose to expend effort in pursuit of the greater reward (959). Later studies by other groups have also established that dopamine depletion does not affect the hedonic response to reward (960), or preference for reward (961). Furthermore, the reduction in effort seen following dopamine antagonism is not seen after glutamatergic (962) or serotonergic alterations (963, 964), but is seen following manipulations of other neurochemical systems that are known to affect dopaminergic function such as estradiol (965), and adenosine (966-972). Moreover, disruption of regions interconnected with the NAc, such as the ventral pallidum, also produce biases in effort-based choice (966, 973). In addition, increasing dopamine levels via amphetamine increases motivated behaviour and also blunts the alteration caused by dopamine antagonists (974). Elevations in endogenous dopamine levels within the NAc have been found to scale with the magnitude of reward value (975). Other studies have also shown that this bias away from effort cannot be explained by motivational state (976). Interestingly, in HE and LE situations where rewards are equal, endogenous dopamine levels within the NAc are lower in response to the HE condition (930, 977). Based on this, a transgenic mouse model that overexpresses dopamine D2 receptors has been developed to model the negative symptoms of schizophrenia (978). Specially, these rodents are found to have intact hedonic reaction (i.e. reward valuation) but impaired incentive motivation (i.e. shift away from HE/HR preference to more LE/LR), perhaps reflecting a deficit in effort computation. Dopaminergic receptor expression, though, within the NAc has not been found to be associated with effort-based decision making (979). Hence, mesolimbic dopamine levels seem critical in the computation of effort costs during cost-benefit decision making (Figure 1-5) (491, 908, 980-984).
Figure 1-5. Theoretical model relating neurobiological functioning with economic parameters related to cost-benefit decision making

A single trajectory represents the maximum effort cost an individual is willing to incur for a given reward. Of note, the trajectories follow a hyperbolic curve. This model is adapted from Phillips et al. (2007) who proposed that differing levels of nucleus accumbens dopamine modulate willingness to expend effort for reward (980). In their model, the grey (normal) curve reflects a basal level of dopamine; whereas the green (hyperactive) curve reflects an increase, and the red (hypoactive) curve reflects a decrease in dopamine. We propose an extension of this model beyond only dopamine to encompass functioning within the entire DA-related neural circuit, including the anterior cingulate cortex. It should be emphasized that this model is theoretical.
1.3.4.1.2 Neuroanatomical Basis of Effort

The basal ganglia has major inputs from the neocortex, suggesting a role for key cortical regions in motivated behaviour (985). For example, lesions to the anterior cingulate cortex (ACC) have been shown to bias away from expending effort for larger rewards (986-988). Of note, the neural substrates of other response costs, such as temporal delay in reward receipt, are separable from those underlying physical effort costs (963, 989); thus, there is some specificity of processing effort costs within the ACC. Other prefrontal regions, such as the orbitofrontal cortex (OFC) appear linked to other value-based processes (914, 990); studies that ablate the OFC have not shown consistent impairments in effort-based decision making (989). Moreover, regions interconnected with the ACC such as the amygdala are also implicated in effort-based decision making (991, 992). Beyond lesion studies, in vivo studies employing micro positron emission tomography and fluorodeoxyglucose in rats performing an effort-based decision making task show that ACC activity covaries with decisions to expend effort (993). Further, neural firing patterns within the ACC measured in rats making effort-based decisions has been shown to vary with decisions to expend effort for reward, specifically encoding effort discounted value of the reward (994-996).

1.3.4.1.3 Neural Circuitry Underlying Effort Cost Computations

Given the roles of both striatal dopamine and ACC function in effort-based decision making, one may speculate that these regions either process this decision together through direct connectivity or, alternatively, that these neuroanatomical nodes both process this information redundantly. There is preliminary evidence in support of this contention from a study where the connection between the ACC and NAc was lesioned. Results indicated similar reductions in effort, as observed after a specific lesion to the NAc (997). This suggests that the ACC and NAc process this information in a circuit rather than in parallel. Moreover, dopaminergic functioning in the ACC has also been implicated (998, 999), but null findings have also been reported (1000).

It may seem that we have exclusively focused on role of dopamine and ACC in effort-based decision making and neglected other neurochemical and cortical regions. This is in fact not the case. The literature on this topic has been consistent with findings of effort-based impairments
following dopaminergic or ACC dysfunction; although some contradictory evidence exists (988, 1001). Moreover, investigations into other neurochemical systems and other cortical, specifically prefrontal, regions have been negative (1002). These other systems do process reward-related variables and therefore have an effect on decision making (911, 915, 920). While this does not mean that these other systems are not important for other portions of motivation processing (Figure 1-4), this does suggest that based on the current literature other systems may not be necessary for the processing of effort. To this end, exhaustive studies examining all neurochemical systems have not yet been performed, and therefore future studies may shed greater light on this issue.

1.3.4.2 Human Studies

1.3.4.2.1 Behavioural Studies Employing Translational Paradigms in Healthy Volunteers

A few studies have employed the PR task in humans. One study used a lever-press response for monetary rewards in children, and found that break-points varied by age and sex (1003). This same group has also reported using this task in children with attention deficit/hyperactivity disorder (ADHD), demonstrating in a cross-over design that a psychostimulant enhanced break-point (1004). This increase in motivation for reward following psychostimulant administration (increasing dopamine levels, among other monoamines) is consistent with the pre-clinical literature. Another study used cigarettes as a reward within a PR task in a sample of smokers (1005), and reported that break-points were reduced following acute phenylalanine/tyrosine depletion (i.e. reducing dopamine levels) compared to placebo. These studies employing a human PR task also highlight the importance of dopamine in effort expenditure, paralleling the pre-clinical literature.

Recently, an effort-based decision making paradigm has been developed for humans (1006). In this task, participants choose to repeatedly press a button on a computer with a finger from their dominant-hand for a lower reward (LE/LR) or repeatedly press a button for longer with a finger from their non-dominant hand for a greater reward (HE/HR). Analogous to pre-clinical studies, the proportion of trials where the participants opt to expend a greater amount of effort is taken as a measure of motivation. This paradigm has since been used in pharmacological studies
demonstrating that amphetamine, but not caffeine, increases the propensity to select high effort trials (1007, 1008). In addition, a positron emission tomography study with a pharmacological challenge to the dopaminergic system found that individuals’ decisions to expend effort inversely correlated with dopamine release in the anterior insula (1009). It is of note that this study did not find a relationship between effortful decisions and dopamine levels within the ventral striatum (NAc); however, a more restrictive region-of-interest analysis of the ventral striatum (NAc) was not carried out.

1.3.4.2.2 Behavioural Studies Employing Translational Paradigms in Psychiatric Patients

Studies employing translational paradigms to assess motivation in patients with neuropsychiatric disorders are quite recent, with reports being published within the last few years. One study employed the Treadway monetary effort-based decision making task in patients with major depressive disorder (1010). In this study, patients were found to be less willing to expend effort for a greater reward (HE/HR decision) relative to healthy volunteers. Furthermore, statistical models revealed that patients utilized reward information less effectively, suggesting that patients demonstrate deficits in multiple nodes of the motivational network (Figure 1-4) that may include reward prediction, reward valuation and effort computation. Another study employed the same task in a sample of high-functioning individuals with autism spectrum disorders, reporting that patients were more likely to expend effort for monetary reward than healthy control subjects (1011). Subsequent analyses revealed that this increased effort expenditure was related to repetitive behaviour symptoms, highlighting the complexity involved in studying effort in patient populations as well as the need to control for potential confounding variables.

1.3.4.2.3 Other Behavioural and Imaging Studies

Other paradigms exploring the neurobiology of effort have also been employed in humans, although these tasks were not developed from pre-clinical models. It should also be noted that these studies do not proxy effort computations per se; rather, they explore the neural substrates of the amalgamated motivational process, including reward prediction and reward valuation (Figure
1-4). One behavioural study using levodopa in healthy volunteers found that increasing dopamine levels resulted in subjects' elevating their subjective value estimations of future rewards (1012). Another study employed a task where humorous cartoons were used as a reward, with participants having to button-press for this reward (1013, 1014). Patients with major depression were found to like the cartoons just as much as healthy controls, but failed to exert effort in pursuit of the reward (1013). In another study, participants were presented with a coin of either large or small monetary value and asked to apply force to a hand grip (1015), with the instructions that the more force they exerted, the more reward they would receive. Investigators found that brain activity, as measured by the blood-oxygen level dependant (BOLD) signal from functional magnetic resonance imaging (fMRI), is modulated in the NAc and ventral pallidum in anticipation of high effort versus low effort. Another behavioural study by this group found that patients with striato-pallidal lesions and auto-activation deficit, a syndrome defined by a loss of self-initiated behaviour and extreme apathy (1016), were unable to modulate the amount of force they exerted despite subjectively valuing greater rewards more (1017). Another behavioural study by this same group found similar deficits in effort modulation among patients with major depressive disorder (1018). These investigations suggest that the ventral striatum and associated ventral pallidal region are important in translating cost-benefit decisions into motor action (1019).

A small number of fMRI studies have been conducted along these same lines. In one study, participants were shown images that they had previously learned were associated with high/low effort and either high/low reward (1020). Notably, participants did not choose to expend effort but, instead, responded to previously learned cues; results indicated that the ventral striatum/NAc BOLD signal encoded a value representing the expected reward discounted by the amount of effort to be invested. Further, the ACC was found to encode the interaction between expected reward and effort cost. Other regions such as the orbital frontal cortex and insula encoded only the reward value. From these studies, it appears that the ACC-NAc circuit is not only important for effort cost computations, but also in the integrations of this information with reward value (i.e. cost-benefit integration).

In another study employing a similar hand-grip procedure, participants were given the option to expend effort (1021), with results indicating NAc BOLD activity encoded an interaction between reward value and effort. Interestingly, ACC activity when choosing to expend a greater amount
of effort was correlated with a personality trait measure of persistence. In another study employing arousing stimuli as a reward, participants were given the option to expend greater effort by way of a harder hand-grip for a larger reward (HE/HR) or expend less effort for a smaller reward (LE/HR) (1022). In this study, duration of viewing time of the arousing stimuli was set as the reward. Findings indicated that activity within the ACC and insular cortex accounted for decisions of whether to expend physical effort, and that the neural substrates of other costs such as temporal delay were distinct. Taken together, studies with healthy human subjects show that ACC and NAc activity are important for effort-based decision making. However, other brain regions such as the insula, orbital frontal cortex and ventral pallidum are also implicated. It is of note that many of the above mentioned fMRI studies employed a univariate statistical analysis approach, which yields information for each brain region independently. Although some studies used a hypothesis-driven region-of-interest univariate analysis and others a model-based approach, the majority did not employ such techniques. Accordingly, inferences about the connectivity between brain regions, as well as any inference of a neural network underlying these processes, remain to be seen. As of yet, the available data suggest a potential modular role of the ACC and NAc in coding effort costs in humans. In addition, dopaminergic function seems to be important for human computation of effort cost, although the evidence is limited to several behavioural studies involving pharmacological manipulations and one imaging study. Imaging studies coupled with pharmacological challenges are clearly warranted; indeed, such pharmaco-imaging studies have considerably advanced our knowledge regarding dopamine's role in reward prediction in humans (1023).

1.3.5 Effort and Motivation in Schizophrenia

1.3.5.1 Effort Cost Computations in Schizophrenia

There is one recently published study assessing effort cost computations in patients with schizophrenia (904). This study employed a paradigm similar to the Treadway monetary effort-based decision making task, where participants chose to complete HE/HR or LE/LR trials. This task also utilizes button presses as physical effort and money as the incentive; notably greater effort is defined as a greater number of button presses. The primary finding in this study was that patients with schizophrenia opted to complete HE/HR trials less often than healthy controls when
the reward value was large. Moreover, this deficit in willingness to expend effort for reward was more pronounced in patients with more severe overall negative symptoms. Interestingly, willingness to expend effort was not related to amotivation measured using a clinical rating scale (572). The study also found that patients completed the tasks with less vigor and overall took longer to complete the task relative to healthy controls; however, these findings may be partially associated with medication-related psychomotor slowing. Willingness to expend effort was related to global neurocognitive functioning, a finding that is consistent with other work demonstrating a relationship between apathy and cognition (712, 850, 1024). This relationship may partially be explained by the role of effort in neurocognitive test performance (1025-1027), which is discussed in greater detail below.

At any rate, the results from this study suggest that people with schizophrenia might have impairments in effort cost computations in the context of cost-benefit decisions involving physical effort and monetary reward. The benefit or valuation side of the equation was equated objectively by offering the same monetary incentive; subjective valuations of the monetary incentive were not assessed. Indeed, the authors do interpret their finding of reduced effort expenditure as possibly reflecting a deficit in value representation. Future work should also assess the generalizability of these findings to other rewards (e.g. food, humour, sex, drugs); in fact, it has been shown that the neural substrates involved in processing reward value may be partially unique for primary versus secondary rewards (1028). Moreover, the decreased willingness to expend effort observed might be related to some mediator variable that was not evaluated in this particular study such as tolerability to delay, reward anticipation, and/or personality factors, to name a few. The multi-faceted nature of motivation (Figure 1-4) as well as the abundance of reward/motivation related deficits found in individuals with schizophrenia underscores the need for a comprehensive approach to studying effort in schizophrenia.

### 1.3.5.2 Other Reward-related Impairments in Schizophrenia: Behavioural Findings

It is unlikely that individuals with mental illness have a single deficit in one computation within the motivational process. Schizophrenia, for example, has been associated with abnormalities in self-report intrinsic motivation (1029-1031), self-report apathy (607, 1032), self-reported recall
of experience of pleasure (586, 1030, 1033-1045), motivated action (1046-1049), reward learning (1050-1054), reward prediction (1046, 1055, 1056), reward anticipation (1057-1061), reward exploration (1055), responsiveness to reward receipt (1062), neural response to reward (1063-1070), value representations (1071), neural encoding of goal-directed behaviour (1072), tolerability of temporal delays in reward receipt (1073, 1074), impulsivity (1045, 1075-1077), consistent decision-making (1078), strategic decision-making (1079-1085), decision-making biases (1086, 1087), cognitive-affective integration (902, 1088, 1089), prospection (1090-1093), planning or executive functions (365, 432, 1094), contextual processing (1095-1097), and working memory (366, 436), amongst other processes. Conspicuously, hedonic experience derived from the consummation of reward seems to be intact in individuals with schizophrenia (1033, 1034, 1078, 1098-1100), suggesting that patients are, by the traditional definition (1101), not anhedonic (1102). These investigations have been conducted independently, and there has not yet been an effort to comprehensively assess multiple aspects of the motivational process in the same individuals with schizophrenia. By assessing these other constructs, researchers can control for these variables in the design of their study (e.g. recruit samples matched for income and/or subjective valuation of reward) and/or in their statistical analysis (e.g. add cognitive deficits as covariates). Such a comprehensive approach, effectively limiting confounding variables, may be better suited to uncovering the true neurobiology of effort cost computations. Notably, the clinical presentation of amotivation or apathy may result from impairment in effort cost computations, a deficit in any stage of the motivational process including the domains mentioned above, or an interaction between multiple domains (Figure 1-4). It may well be that the exact computational cause of the clinical presentation of amotivation/apathy differs between patients. Parsing the neurobiology of these computations may assist in discerning the underlying cause of amotivation in patients with schizophrenia.

A recent NIMH initiative, the Research Domain Criteria (RDoC), provides a framework to approach such a comprehensive assessment (1103-1105). The RDoC initiative was created to better understand core neurobiological processes that underlie behaviour along a dimension (i.e. including pathological and non-pathological behaviour). Such an approach could inform the next generation of nosology in psychiatric research based on translational neuroscience. Within the RDoC framework are various behaviours, as well as potential methods to tap into each, including genetic, neurochemical and subjective experience, to name a few. The approach behaviour
domain is of particular interest to the current discussion as this domain includes constructs of reward valuation, willingness to work (i.e. effort cost computation), reward expectation and action selection. The NIMH has also provided consensus based approaches to tap into each of these subdomains of motivated behaviour, thereby setting the stage for a comprehensive investigation into the multi-faceted construct of motivation. It should be noted that the assessments suggested to tap into any one of the subdomains may actually tax multiple processes that are required before and after that process of interest is employed. For example, in assessing reward anticipation an organism must first provide an intrinsic value to the reward; assessment of any single construct is therefore confounded by the entire process, at least at the behavioural level. Such processes might better be dissociated at the level of neural functioning. These concerns apply to the study of effort in all populations, but are particularly relevant in populations with diffuse neural deficits, as is likely the case in schizophrenia (356, 358).

1.3.5.3 Other Reward-related Impairments in Schizophrenia: Neurobiological Findings

Currently, there are no published reports of neurobiological investigations specifically focused on effort computation or amotivation in schizophrenia per se. In fact, there is only one published report employing a translational paradigm in this population to assess effort (904); however, some studies have attempted to unveil the neural substrates indirectly.

Several fMRI investigations have been carried out in patients with schizophrenia employing a reward anticipation paradigm. In this paradigm, known as the monetary incentive delay task, participants are presented with a cue denoting reward value after which there is a delay (1106, 1107). Following the delay, participants respond via button-press in order to receive the reward. Neural activity (i.e. changes in BOLD response) following cue presentation, but preceding the response, is taken as coding for reward anticipation. One such study found that ventral striatal (NAc) activity in anticipation of reward was inversely related to SANS amotivation scores (1064). In another investigation, reward anticipation signals within the same region were inversely correlated with amotivation scores assessed with the AES, whereas neural activity during reward outcome was related to depression scores (761). Although these studies do not
comment on effort computation per se, they do relate neural signals to more generally defined clinical amotivation.

Some studies have also explored the neural correlates of activity in patients with schizophrenia. One study found a correlation between mean activity as measured by actigraphy and ACC volumes (893). Along similar lines, another report found a correlation between actigraphic measurements and diffusion tensor imaging based metrics of white matter integrity in motor regions (895). Another study by the same group found correlations between their motor measurements and MRI based cerebral blood flow in the basal ganglia and prefrontal regions including the ACC (896).

1.3.5.4 Cognitive Effort Costs

As noted above, there is only a single study on physical effort computations that has evaluated this construct in individuals with schizophrenia (904), although numerous investigations have studied cognitive functioning. Decision making experiments involving cognitive (effortful) demands have suggested that cognitive demand carries an intrinsic effort cost (1108-1112). To this point, an fMRI study demonstrated that activity in the NAc was inversely modulated by mental effort costs, and further that NAc activity levels correlated with activity within the ACC during the previous trial (1113). Another recent fMRI study in healthy volunteers found that ventral striatal (NAc) BOLD activity encoded both physical (hand-grip) and cognitive effort (attentional demand) (1114). Furthermore, there is some pre-clinical work indicating a dopaminergic influence on cognitive effort costs (1115).

Interestingly, the ACC emerges as a key node underlying task difficulty across cognitive tasks in healthy volunteers (1116-1118) and in patients with schizophrenia (1119, 1120). Although there are many studies employing cognitive tasks in patients with schizophrenia, we shall only highlight a few. One investigation employed a cognitive control task involving responses to congruent and incongruent stimuli (1121), reporting decreased activity within the ACC in response to incongruent stimuli, as well as in error trials, in patients with schizophrenia relative to healthy controls. In addition, patients did not modulate their behaviour following errors or incongruent stimuli, possibly reflecting a diminished effort to do so, a finding that is consistent
with previous behavioural studies (1122, 1123). Another study using an attention task showed similar blunting of ACC activity in response to errors in patients with schizophrenia relative to healthy volunteers (1124). It has also been shown that activity within the ACC is associated with rates of error commission (1125, 1126). A recent meta-analysis of fMRI studies employing an executive functioning task (i.e. requiring effortful responses) found a reduction in ACC activity in response to such tasks in individuals with schizophrenia (365). Beyond functional neuroimaging studies, several studies have noted abnormalities in ACC structure in schizophrenia (349-351, 1127), as well as neurochemical alterations (329, 1128-1130). Future studies aiming to disambiguate the neural correlates of mental effort costs (in schizophrenia) should consider potential confounders such as cognitive capacity, error rates, and delays in completion time that may differ between high versus low cognitive demand tasks.

There is also some evidence suggesting that mental effort may influence cognitive performance. One study has reported that poor mental effort accounted for a sizeable portion of variance in neuropsychological test performance (1131), a finding that has been subsequently replicated (1132). Interestingly, some studies have suggested that offering incentives for neurocognitive performance, and therefore increasing the inherent value of the task, leads to superior neurocognitive test performance, suggesting a key role for effort (1047, 1133-1137); however, contradictory findings have also been reported (1138-1140). Abnormalities in effortful responding in schizophrenia have also been linked to physiological anomalies (1141). Thus, diminished conation may account for several phenomenological features of schizophrenia.

It is worth noting that the ACC, particularly the dorsal ACC, has been found to be related to effort-based decision making as reviewed herein; however, beyond effort computations, the ACC has been associated with various other cognitive processes including, but not limited to, processing of errors, conflicts and pain (1142-1150). It is not known whether the same regions within the ACC underlie effort computations and cognitive control, or whether distinct subregions of the ACC subserve these processes. It may be that cognitive control carries an intrinsic effort cost which is computed, stored and/or integrated within the ACC (1151). If this is the case, a functional role of the ACC may be effort cost computation irrespective of the modality of cost (e.g. physical, cognitive demand) - this remains to be established empirically.
1.3.5.5 Toward a Neural Circuitry Underlying Effort in Schizophrenia

Taken together, there have not been any published reports of direct investigations on the neural substrates of effort computations in schizophrenia to date. A better understanding of these deficits may lay the groundwork to improve the downstream functional consequences (607, 850, 876, 891). Despite there being no direct investigation, a preliminary synthesis of pre-clinical work, as well as studies in healthy human volunteers, is possible, which can help shape future investigations and create testable hypotheses. This synthesis is in essence analogous to circuits thought to underlie apathy in the neurology literature (711, 1152); however, we attempt to move beyond the classical emphasis on modular processing among brain regions towards a more circuit based framework. It should be noted that any synthesis should be applicable to other neuropsychiatric conditions that include abnormalities in goal-directed behaviour such as major depressive disorder (1153-1155); future work in this regard should aim to parse the relative contribution of effort costs, as well as that of other aspects of motivational processing (Figure 1-4), in producing clinical amotivation/apathy across disorders.

From the available literature, we believe that connectivity between the ACC and NAc, rather than modular functioning of either structure in its own right, to be central to the computation of effort. This can be tested in future studies by examining functional connectivity metrics, especially effective connectivity from the ACC to the NAc, and regressing this metric with willingness to expend effort measure derived from an effort-based decision making task. At this point, it is unclear whether this connection is subserved by dopaminergic or other neurochemical (e.g. glutamatergic) systems. It does seem clear that within the NAc dopamine functioning is of critical importance, and any manipulations of dopamine should theoretically affect behavioural measures of effort.

1.3.6 Implications for Future Research and Treatment

1.3.6.1 Dopamine, Effort, and Antipsychotic Medications

Over fifty years ago, the discovery of chlorpromazine's effectiveness for the positive symptoms of schizophrenia heralded a new era of biological psychiatry. This discovery of dopamine D2 receptor antagonism having therapeutic value for psychosis revolutionized the treatment of
schizophrenia but, ironically, may also have impeded our progress in understanding and
developing treatments for negative symptoms. Years later, it was established that these same
drugs induce secondary negative symptoms (488, 496, 519, 1156, 1157), confounding any efforts
to study amotivation at the behavioural level in individuals treated with these medications. This
effect appears mediated by dopamine D2 antagonism (511, 1158, 1159), considered the
cornerstone of treatment for positive symptoms in schizophrenia and a feature that characterizes
all antipsychotics, albeit to varying degrees (227).

Given the role of antipsychotics in biasing effort-based decision making in pre-clinical research,
it follows that patients with schizophrenia might demonstrate impairments in effort cost
computations that are medication related. The extent of this should be determined in future
work. Indeed, antipsychotic medications have been shown to affect reward related neural activity
in healthy volunteers (1160, 1161), and patients with schizophrenia (1162-1164). Nonetheless, it
seems unlikely that motivational deficits and impairments in effort are purely related to
antipsychotic action, as these deficits have been described in the pre-neuroleptic era (14, 23) and
are present during the prodromal phase of the illness (199, 1165).

1.3.6.2 Effort and Amotivation as Treatment Outcomes

Amotivation and impairments in effort cost computations are subsumed under the heterogeneous
construct of negative symptoms; hence, treatments aimed at improving effort cost computation
deficits would, by definition, improve negative symptoms. But, by the same token,
improvements in negative symptoms broadly defined are not commensurate with improvements
in amotivation specifically (i.e. other negative symptoms may be affected). Although studies to
date have assessed treatment effects on negative symptoms more broadly defined, moving
forward the field would benefit from assessing treatment effects on amotivation specifically.
This concern has been raised by the MATRICS statement on negative symptoms (471), as well
as in the structure of the newer negative symptom scales for schizophrenia (572, 573). There are
currently no published studies that have specifically assessed effects of treatment on effort
computations or level of amotivation, we will nevertheless review treatment studies evaluating
treatment effects on negative symptoms.
1.3.6.3 Dopaminergic Treatments

Throughout this review, reference has been made to the role of dopamine hypofunctioning in biasing decisions away from expending effort. That increasing dopamine levels would improve amotivation is intuitively reasonable; indeed the benefits of dopaminergic enhancement, through for example dopamine agonists, on negative symptom psychopathology has been long recognized (1166-1168). However, such a strategy carries the potential risk of worsening psychotic symptoms (1169). While it has been proposed that increasing dopamine levels in conjunction with concurrent dopamine D2 antagonism attenuates this risk (1167, 1170-1174), controlled trials are needed. Along these lines, there does seem to be several registered trials examining the therapeutic value of dopamine agonists (1175), and there is some preliminary evidence supporting such an approach. One open-label study of lisdextroamphatemine (which acts to increase dopamine levels) for predominant negative symptoms in schizophrenia found that SANS total scores significantly improved following 10 weeks of treatment, without any significant worsening of psychosis (462). In another trial, use of a monoamine oxidase inhibitor, which increases dopamine levels, was shown to reduce negative symptoms (1176).

Other pilot studies to date have produced equivocal findings. For example, one study evaluating the efficacy of adjunctive dopamine D3 agonism found modest benefits for negative symptoms as a whole (1177). This trial was not specifically designed to evaluate negative symptoms, though, and did not employ the SANS or longer term follow-up. To this last point, it has been argued that trials involving negative symptoms actually extend beyond conventional follow-up periods as improvement on this domain may occur more gradually (471, 1178). One study examined the effect of a single dose of a D1 agonist and found no difference in overall negative symptoms as a whole (1179); however, the effects of sustained D1 agonism on amotivation remain unknown. In another study, the stimulant drug mazindol did not demonstrate a therapeutic effect in terms of overall negative symptoms (1180). Furthermore, increasing norepinephrine levels through reuptake inhibitors also does not seem to affect negative symptom psychopathology (1181).
1.3.6.4 Neuromodulation Treatments

Trials have also been conducted evaluating the efficacy of repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex in ameliorating negative symptoms; stimulation of this region has been shown to increase dopamine release in the striatum, albeit not in the NAc (1182). There is preliminary evidence that rTMS is effective in individuals with prominent negative symptoms (1183, 1184), although some findings are contradictory (1185), leading to the call for further research of this treatment modality (307). Possibly a more focused target, such as the ACC, may prove to be an effective treatment option.

Interventions targeting the NAc are warranted given the prominent role of NAc functioning in predicting SANS amotivation scores in individuals with schizophrenia, in addition to the wealth of pre-clinical studies implicating this region. There is, in fact, a registered pilot study investigating the application of deep brain stimulation (DBS) to the NAc for patients with schizophrenia manifesting predominant negative symptoms (clinicaltrials.gov identifier #NCT01725334). Offering further support for such an approach is evidence that DBS to the NAc in patients with major depression improves reward-related symptoms such as anhedonia (1186-1188).

1.3.6.5 Cognitive Treatments

Beyond pharmacological treatments, cognitive therapy has been proposed as a viable option. This is not unreasonable given the burgeoning interest in cognitive schemas that might underlie negative symptoms (1189). Within the motivational process (Figure 1-4), for example, reward prediction and reward valuation processes can potentially be influenced by internal psychological schemas such as defeatist beliefs. It is thought that such cognitions can manifest themselves downstream as clinical amotivation/apathy and reduced willingness to expend effort. In other terms, someone who feels that if they fail at a task they are a failure in general may devalue prospective rewards quite steeply, or perhaps overestimate effort costs. There is, in fact, evidence from a randomized controlled trial that cognitive-behavioural therapy improves SANS amotivation scores in low-functioning patients with schizophrenia (290), a finding that is
consistent with other trials demonstrating a positive effect of such interventions on negative symptoms in general (289).
Chapter 2

2 Overview of Experiments and Hypotheses

This thesis consists of nine individual papers describing studies that advance our understanding of motivation, and deficits therein, in patients with schizophrenia, with a particular emphasis on studying these issues in younger patients who are relatively early in the course of illness. The included studies explore several issues relating to motivational deficits in schizophrenia, including their prognostic value (Chapters 3 and 4), prevalence (Chapter 4), measurement (Chapters 5 and 8), underlying behavioural mechanisms (Chapters 6 and 7), relationship with other domains of illness (Chapters 9 and 10), and response to treatment (Chapter 11).

Eight of the nine chapters have been published or have been accepted for publication in peer-reviewed journals (with the exception of study 5; Chapter 7). Because these studies exist as standalone articles, overlap in presented material is inevitable; material, including the background text, presented in one chapter may overlap with material presented in another, including material presented in the preceding introductory chapter.

2.1 Study One: Amotivation and Functional Outcomes in Early Schizophrenia

2.1.1 Background and Aims

The prognostic value of negative symptoms broadly defined have long been recognized, especially the value of these symptoms for predicting functional outcomes. In response to the growing recognition of negative symptoms as comprising of multiple subdomains, there has been increased interest in the past several years in exploring the differential value of these subdomains and/or individual negative symptoms for predicting functional outcomes. Several studies have suggested that motivational deficits in particular may play a particularly important role in determining outcome. However, the majority of these studies have been carried out with a heterogeneous sample of chronic patients, who have been ill for many years before the time of assessment, and whether these findings extend to younger patients who early in their disease
course, and have not been subjected to external factors that may confound that assessment of negative symptoms (e.g., years of illness and unemployment), remains to be established. This study explored the role of motivational deficits, along with other known predictors of outcome (e.g., cognitive impairment), in predicting cross-sectional outcomes in a sample of early-course schizophrenia patients.

2.1.2 Hypotheses

Consistent with findings in more chronic samples of patients with schizophrenia, it was hypothesized that motivational deficits would have a significant association with cross-sectional functional outcome. We further hypothesized that other variables would not demonstrate predictive value once the contribution of motivational deficits had been taken into account.

2.2 Study Two: Motivational Deficits in Early Schizophrenia: Prevalent, Persistent, and Key Determinants of Functional Outcome

2.2.1 Background and Aims

On the heels of the findings from our initial study (study one), we sought to replicate and extend our findings on the importance of motivational deficits in terms of predicting functional outcome in early schizophrenia. In this study, we included a larger sample of patients recruited from a range of sources including both tertiary and primary care settings. In addition to cross-sectional relationships, we also explored the value of motivational deficits in predicting short-term (i.e., 6-month) longitudinal functioning, as well as longitudinal inter-relationships. Given the large and heterogeneous sample of patients included, we also sought to document the prevalence of motivational deficits in the early-course of the illness.
2.2.2 Hypotheses

Based on our initial findings, it was hypothesized that motivational deficits would again emerge as significant predictors of both cross-sectional and longitudinal functional outcomes. It was further hypothesized the changes in motivational deficits would significantly predict changes in functional status, such that patients with increases in motivation would evidence concurrent increases in functioning, whereas decrements in motivation would translate to decreases in functioning over the follow-up period. Also consistent with our initial findings, we hypothesized that other variables such as cognitive impairments would not demonstrate significant predictive value over and above the contribution made by motivational deficits. We also hypothesized that motivational deficits (to varying degrees of severity) would be highly prevalent in early-course patients, but would not characterize all patients, and only a minority of patients would evidence severe motivational deficits.

2.3 Study Three: Measuring Motivation in People with Schizophrenia

2.3.1 Background and Aims

Clinical rating scales are the mainstay of psychiatric measurement. There exist several rating scales that are either focused exclusively on the measurement of motivational deficits or include individual items that tap into this construct. Investigations into the motivational deficits in schizophrenia have largely relied on such clinical rating scales for the quantification of motivational deficit severity; however, there is little consensus on the optimal instrument to be used. Therefore, investigators have employed various different rating scales, and there exists little systematic evidence of the degree of overlap or convergence between these scales. This study examined the degree of overlap between commonly used measures of motivational deficit in patients schizophrenia, as further explored their discriminant validity from other clinical variables.
2.3.2 Hypotheses

It was hypothesized that each of the motivational deficits would be highly correlated, suggestive of each tapping into the same underlying construct. It was further hypothesized that each of these measures would not correlate strongly with other measures (e.g., depressive symptoms), suggestive of discriminant validity.

2.4 Study Four: Incentive Motivation Deficits in Schizophrenia Reflect Effort Computation Impairments During Cost-Benefit Decision Making

2.4.1 Background and Aims

Given the importance and burden of negative symptoms and motivational deficits in particular, there has been a concerted effort in the field to examine possible underlying mechanisms. Most of these investigations have explored reward processing, given its intuitive and empirically demonstrated links to motivation in the pre-clinical literature. Over the years, and through many individual investigations, several reward-related impairments have been noted in patients with schizophrenia, which correlate to negative symptom burden to varying degrees. There has not been a comprehensive examination of several reward processing variables together in patients with schizophrenia, a strategy that would be better suited for isolating specific impairments in individual reward processes. In this study, we sought to behaviourally demonstrate incentive motivation deficits (i.e., reductions in goal-directed approach behaviour) in patients with schizophrenia, while accounting for other reward-related variables that might obfuscate the interpretation of incentive motivation deficits.

2.4.2 Hypotheses

We hypothesized that individuals with schizophrenia would demonstrate deficits in their willingness to expend effort for reward. It was further hypothesized that this deficit in incentive motivation would not be accounted for by other reward variables, such as reward learning capacity, or valuation of the reward, suggestive of an impairment instead in computation of effort.
cost. Finally, we also hypothesized that individuals' willingness to expend effort in exchange for reward would be related to their level of clinically-rated real-world motivation.

2.5 Study Five: Deconstructing Goal-directed Behaviour: A Concurrent Evaluation of Hedonic Experience, Reward Learning, and Effort Cost Computations in Early Schizophrenia

2.5.1 Background and Aims

This study represents an important extension of the work presented in the previous chapter; namely, we studied multiple reward processes as indexed by objective neuroscience-driven paradigms in patients with schizophrenia. Three processes were studied in particular: (1) hedonic experience or reward valuation was evaluated using an emotion evocation paradigm coupled with in-the-moment reports; (2) reward learning was assessed using feedback-driven metrics from a probabilistic reinforcement learning task; and (3) effort cost computations were evaluated using an effort-based decision making paradigm that accounted for individual differences in motoric ability. We recruited a larger sample of carefully selected patients with a range of clinically defined motivational deficits.

2.5.2 Hypotheses

Consistent with our prior results, we hypothesized that patients with schizophrenia would as a group demonstrate a decreased willingness to expend effort in exchange for reward, and that this difference would not be fully accounted for by potential differences in reward learning or hedonic experience. Moreover, it was also hypothesized that patients willingness to expend effort (i.e., the amount that they discounted reward value by physical effort) would be directly related to their burden of clinical amotivation.
2.6 Study Six: Effort-based Decision Making as an Objective Paradigm for the Assessment of Motivational Deficits in Schizophrenia

2.6.1 Background and Aims

There are several published trials that have examined the efficacy of a range of pharmacologic and non-pharmacologic treatments for both negative and cognitive symptoms of schizophrenia. Treatment trials with cognition as the primary outcome routinely employ standardized performance-based tests as their outcome measure; however, studies with negative symptom endpoints rely on clinical rating scales as their primary outcome measures. In this study, we sought to explore the validity and reliability of an objective paradigm for the assessment of motivational deficits in schizophrenia. Specifically, we examined the test-retest reliability, convergent validity, discriminant validity, and tolerability of an effort-based decision making task in a relatively large sample of patients with schizophrenia.

2.6.2 Hypotheses

It was hypothesized that effort performance would be consistent over time and that there would be minimal changes over time. Specifically, it was hypothesized that the reliability would be similar to standard performance-based cognitive tests routinely used in schizophrenia research. We also hypothesized that effort performance would be related to clinically rated negative symptoms, although the magnitude of overlap between these two measurements would not be large. Beyond a relationship with negative symptom burden, we did not expect a large degree of overlap with other clinical variables such as depressive symptoms. Finally, we hypothesized that patients with schizophrenia would not find the task overly burdensome, and would report that the task was in fact not extremely difficult.
2.7 Study Seven: Effect of Intrinsic Motivation on Cognitive Performance in Schizophrenia: A Pilot Study

2.7.1 Background and Aims

Poor effort and motivation has been shown to impact performance on standard cognitive tests. This relationship has also been documented in patients with schizophrenia, with investigations showing a relationship between these two variables using a range of definitions for poor effort and motivation on the one hand, and cognitive performance on the other. In this study, we explored the relationship between performance on cognitive tests in patients with schizophrenia and the level of motivation these patients endorsed to complete the cognitive testing in particular.

2.7.2 Hypotheses

It was hypothesized the patients level of motivation specifically tied to their interest and perceived value in completing the cognitive testing procedures would be significantly related to their performance on these same tests.

2.8 Study Eight: Motivational Deficits and Cognitive Test Performance in Schizophrenia

2.8.1 Background and Aims

Based on the findings from our previous study (study seven), we sought to replicate and extend our findings on the relationship between motivational deficits and cognitive test performance in patients with schizophrenia. In this study, we included a larger sample of patients recruited from a range of sources including both tertiary and primary care settings. We explored relationships between motivation and global cognition, as well as performance on cognitive tests tapping into a specific domain (e.g., verbal memory, reasoning). In addition to cross-sectional relationships, we also explored longitudinal inter-relationships between changes in motivational deficits on the one hand, and changes in cognitive performance on the other. Finally, to explore the specificity of these findings, we conducted several additional analyses to rule out the idea that a "third"
variable might be accounting for our observed findings (e.g., overall severity of illness, relationship with functioning).

2.8.2 Hypotheses

Based on our previous findings, we again hypothesized that there existed a significant relationship between motivational deficits and cognitive performance, assessed using a composite score (i.e., global cognition) and for performance within individual cognitive domains. It was further hypothesized that changes in motivation would emerge as a significant predictor of changes in cognitive test performance, with increases in motivation translating to improvements in test performance, and decreases in motivation translating to poorer performance over time. We also hypothesized that these cross-sectional and longitudinal inter-relationships would not be fully accounted for by other variables such as the relationship between these two variables and functional outcome, or other domains of illness. In other words, the association between motivation and cognition would represent a specific relationship, rather than one that represents a pseudo-relationship secondary to both of these variables being indicators of more severe illness for example.

2.9 Study Nine: Antipsychotics and Amotivation

2.9.1 Background and Aims

Antipsychotic drugs are thought to produce secondary negative symptoms. There is a wealth of pre-clinical literature employing these medications for the dopaminergic receptor blockade properties, and these same studies have shown that administration of antipsychotic drugs leads to behaviours reflective of motivational deficits in animals, often in a dose-dependent manner. These pre-clinical investigations have however employed acute single-dose paradigms, a scenario that by no means mimics real-world prescription practices of these medications for the treatment of schizophrenia, where these medications are taken routinely over longer periods of time. In this study, we examined whether there exists a dose-dependent relationship between antipsychotic dose and severity of motivational deficits. We also explored whether patients who
were antipsychotic-free, and subsequently treated with antipsychotic medications for a longer period of time (6-months) would evidence changes in their motivational deficit burden.

2.9.2 Hypotheses

Based on the available clinical literature, it was hypothesized that antipsychotic dose would not be related to the degree of motivational deficits experienced by patients with schizophrenia. We further hypothesized that going from an antipsychotic-free state to longer-term treatment with antipsychotics would not necessarily result in worsening of motivational deficit severity.
Chapter 3

3  Amotivation and Functional Outcomes in Early Schizophrenia

Contents of this chapter have been published as: Fervaha G, Foussias G, Agid O, Remington G. Amotivation and functional outcomes in early schizophrenia. Psychiatry Research 2013;210(2):665-668. (891)

Reprinted from Psychiatry Research, 210, Gagan Fervaha, George Foussias, Ofer Agid, Gary Remington, Amotivation and functional outcomes in early schizophrenia, 665-668, 2013, with permission from Elsevier.

3.1 Introduction

Since the early writings of Emil Kraepelin, avolition (i.e. amotivation/apathy) has been considered to be core to the schizophrenic syndrome and its course (14). These symptoms are persistent, refractory to current treatments and contribute significantly to functional decline (471).

Within the negative symptom domain, amotivation or apathy (terms are used interchangeably) has figured a prominent role in predicting outcomes (454). Recent investigations have confirmed a key role of amotivation/apathy in predicting functional outcomes (both cross-sectionally and longitudinally) in first-episode (874, 875) and chronic populations (607, 850, 876). These reports are in line with previous findings indicating negative symptoms in general predict functional outcomes over and above the contributions of other symptoms such as psychosis, depression and cognition (568, 770, 817, 851, 1190). However, these studies have not yet explored the relationship between amotivation specifically and functional outcomes in stable early-course schizophrenia patients. Although negative symptoms can be validly assessed in patients with first-episode psychosis (693), there are nonetheless some conceptual challenges; for example, apathy within a first-episode psychosis sample seems to differ based on diagnosis (e.g. schizophrenia-spectrum versus psychosis not-otherwise-specified) (874), is quite unstable during
the initial year of treatment (1191), and is an unreliable predictor of apathy during clinical stability (1190).

Studying early-course, rather than chronic, patients also indirectly minimizes potential confounds such as chronic disease effects, extended institutionalization and stigma to name a few (815, 1192). Hence, we set out examine the impact of amotivation in predicting functional outcomes, while controlling for other clinical variables, in patients with schizophrenia early in the disease course.

### 3.2 Methods

#### 3.2.1 Participants

Seventeen outpatients with a DSM-IV-TR diagnosis of schizophrenia, confirmed using medical records and the Mini International Neuropsychiatric Interview – Plus edition (1193), participated in the present study. Patients were recruited from outpatients clinics at the Centre for Addiction and Mental Health, Toronto, Ontario. All patients were tested while on a stable dose of antipsychotic medication, with no changes for at least four weeks. Patients were included in the study if they were relatively early in the disease course (age between 18-35 years). Patients were excluded from the study if they: met diagnostic criteria for a current mood disorder or substance use disorder within the past 3 months; had a history of neurological or major medical disease; were experiencing significant akathisia (global rating $>2$ on the Barnes Akathisia Rating Scale) (1194) or extrapyramidal symptoms (3 or more ratings of $>2$ on the Simpson-Angus Rating Scale) (1195). The study protocol was approved by the research ethics board at the Centre for Addiction and Mental Health and all participants provided written informed consent.

#### 3.2.2 Instruments and Procedure

Amotivation was assessed using the Apathy Evaluation Scale – Clinician version (AES-C) (692). Positive and negative symptom severity was evaluated using the Scale for the Assessment of Positive Symptoms (614), and the Scale for the Assessment of Negative Symptoms (SANS) (472), respectively. Expressive negative symptoms were derived from the SANS by summing the
affective flattening subscale (excluding the global item) and the poverty of speech item. Depressive symptoms were measured with the Calgary Depression Scale for Schizophrenia (649). Neurocognition was evaluated using the MATRICS Consensus Cognitive Battery (1196). Psychosocial functioning was assessed with an abbreviated version of the Quality of Life Scale (QLS-A) (868, 1197). In addition, due to concerns regarding potential overlap between some QLS-A items and negative symptoms, the Social and Occupational Functioning Assessment Scale (SOFAS) (1198) was employed as a secondary measure of functioning.

Following diagnostic assessment, participants’ psychopathology was rated by a single rater during a single baseline visit. The AES-C was administered by either the same (N = 9) or an independent rater (N = 8). Inter-rater agreement (i.e. scores within 1 point) between raters was over 90%. Cognitive testing was completed on a separate visit, within two weeks of baseline, to limit potential mood-induction or fatigue effects.

3.2.3 Statistical Analysis

Statistical analyses were carried out using SPSS v.15 (SPSS Inc., Chicago, IL). Data distributions were examined for normality and skew. Depression scores, psychotic symptoms and expressive negative symptoms demonstrated positive skew; hence, these variables were square-root transformed before analyses. All descriptive data reported are of original untransformed data.

Bivariate correlations were computed using Pearson’s product-moment coefficients to examine potential relationships between functioning and clinical variables. Partial correlations were also computed to determine the impact of covariates such as AES-C rater on the relationship between amotivation and functioning. Next, hierarchical multiple regression models were calculated to assess the independent contribution of amotivation, while controlling for other clinical variables, for predicting functioning. All tests were two-tailed and statistical significance was set at $\alpha<0.05$. 
3.3 Results

Demographic and clinical information of the study sample are reported in Table 3-1. Bivariate correlations between the functioning measures and AES-C are depicted in Figure 3-1, while relationships with other clinical variables are reported in Table 3-2. Partial correlations between apathy and functioning, controlling for duration of illness and AES-C rater, did not alter the results (QLS-A: $r = -0.65, p = 0.01$; SOFAS: $r = -0.56, p = 0.03$). Furthermore, restricting our sample to individuals whose duration of illness was 5 years or less did not change the results ($n = 10$; QLS-A: $r = -0.69, p = 0.03$; SOFAS: $r = -0.68, p = 0.03$). Hierarchical regression models revealed that amotivation was the strongest predictor of functioning, with no independent contributions from other variables (Table 3-3).

Table 3-1. Demographic and clinical characteristics of study sample

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) or N</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years</td>
<td>27.8 (4.5)</td>
<td>21-35</td>
</tr>
<tr>
<td>Duration of Illness, Years</td>
<td>5.8 (3.5)</td>
<td>1-12</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>11/6</td>
<td>-</td>
</tr>
<tr>
<td>Ethnicity, Number</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Caucasian</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>African-Canadian</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>South-Asian</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>East-Asian</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>CPZ Eq.</td>
<td>468.5 (227.5)</td>
<td>131-874</td>
</tr>
<tr>
<td>SAPS (Total)</td>
<td>19.5 (23.4)</td>
<td>0-77</td>
</tr>
<tr>
<td>Measure</td>
<td>Median (Q1-Q3)</td>
<td>Range</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>SANS (Total)</td>
<td>28.8 (13.1)</td>
<td>6-56</td>
</tr>
<tr>
<td>SANS-Expressive</td>
<td>9.6 (8.0)</td>
<td>0-23</td>
</tr>
<tr>
<td>AES-C (Total)</td>
<td>20.2 (9.6)</td>
<td>7-40</td>
</tr>
<tr>
<td>CDSS (Total)</td>
<td>3.9 (4.1)</td>
<td>0-14</td>
</tr>
<tr>
<td>MCCB (Composite T-score)</td>
<td>27.3 (12.9)</td>
<td>0-44</td>
</tr>
<tr>
<td>QLS-A (Total)</td>
<td>3.8 (0.8)</td>
<td>2.3-4.9</td>
</tr>
<tr>
<td>SOFAS</td>
<td>59.5 (15.9)</td>
<td>23-85</td>
</tr>
</tbody>
</table>

Abbreviations: SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; CDSS: Calgary Depression Scale for Schizophrenia; MCCB: MATRICS Consensus Cognitive Battery; AES-C: Apathy Evaluation Scale – Clinician version; QLS-A: Quality of Life Scale – Abbreviated; SOFAS: Social and Occupational Functioning Assessment Scale. CPZ Eq.: Chlorpromazine equivalents based on Andreasen et al. (1199).

Table 3-2. Bivariate correlations between functioning measures and clinical variables

<table>
<thead>
<tr>
<th></th>
<th>QLS-A</th>
<th>SOFAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES-C</td>
<td>-0.72**</td>
<td>-0.62**</td>
</tr>
<tr>
<td>SANS-E</td>
<td>-0.45</td>
<td>-0.48*</td>
</tr>
<tr>
<td>CDSS</td>
<td>-0.40</td>
<td>-0.26</td>
</tr>
<tr>
<td>MCCB</td>
<td>0.21</td>
<td>0.21</td>
</tr>
</tbody>
</table>
### Table 3-3. Hierarchical multiple regression models predicting functioning

<table>
<thead>
<tr>
<th></th>
<th>QLS-A</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>Adj. β</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AES-C</td>
<td>0.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SANS-E</td>
<td></td>
<td>-0.68</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AES-C</td>
<td>0.53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CDSS</td>
<td></td>
<td>-0.68</td>
</tr>
</tbody>
</table>

* *p < 0.05; **p < 0.01

See Table 3-1 for abbreviations; SANS-E: SANS Expressive symptoms subdomain; DUI: Duration of Illness.
<table>
<thead>
<tr>
<th>Model</th>
<th>r</th>
<th>p</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 3</td>
<td>0.58</td>
<td>&lt;0.01</td>
<td>0.47</td>
<td>0.01</td>
</tr>
<tr>
<td>AES-C</td>
<td>-0.76</td>
<td>&lt;0.01</td>
<td>-0.66</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SAPS</td>
<td>-0.26</td>
<td>0.16</td>
<td>-0.29</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.58</td>
<td>&lt;0.01</td>
<td>0.37</td>
<td>0.05</td>
</tr>
<tr>
<td>AES-C</td>
<td>-0.76</td>
<td>&lt;0.01</td>
<td>-0.60</td>
<td>0.02</td>
</tr>
<tr>
<td>MCCB</td>
<td>-0.01</td>
<td>0.98</td>
<td>-0.04</td>
<td>0.86</td>
</tr>
</tbody>
</table>

See Table 3-1 for abbreviations; Adj: Adjusted.

Figure 3-1. Bivariate relationship between amotivation and psychosocial functioning as assessed by: (a) the QLS-A or (b) SOFAS
Note: See Table 3-1 for abbreviations.

3.4 Discussion

The present study examined the impact of amotivation on functional outcomes in individuals with schizophrenia who are relatively early in their disease course. Our results reveal amotivation as the chief predictor of functioning, consistent with and partially replicating previous findings from first-episode (874, 875) and chronic samples (607, 850, 876). This suggests that apathy is intimately tied with functioning across disease course, and also underscores the need for treatment of these persistent impairments (471). Its presence in the early stages of the illness also calls for strategies extending beyond management of positive symptoms from the outset of treatment.

One of the strengths of the study was the use of the AES-C, an instrument specifically designed to assess apathy (692). The AES-C, unlike other scales such as the SANS, measures amotivation by assessing both intrinsic states and objective behaviours, rather than objective behaviours only as in the SANS. Another strength was the employment of two non-redundant functioning scales. Indeed, amotivation robustly predicted functioning, with estimations being invariant to the specific functioning scale. Interestingly, other co-existent negative symptoms (diminished expression domain), depression, psychosis and neurocognition did not contribute to the prediction of functioning independent of apathy. This finding is line with previous reports in chronic samples that have also specifically assessed apathy (850, 876).

A limitation of the current study was the small sample size, which may have limited our power to detect influences from other symptom domains. Nevertheless, the sample size was sufficient to reveal the robust effects of amotivation, which speaks to the relatively large effect size. Moreover, all clinical assessments relied on patient self-report. Future research should re-examine these relationships employing more objective assessments (892, 893). Notwithstanding these limitations, our results affirm a fundamental relationship between amotivation and functioning in schizophrenia. With increasing efforts aimed at ameliorating negative symptoms and improving outcomes, greater attention on the assessment of motivational deficits, as well their underlying neurobiology, may facilitate rehabilitative efforts.
Chapter 4

4 Motivational Deficits in Early Schizophrenia: Prevalent, Persistent, and Key Determinants of Functional Outcome

Contents of this chapter have been published as: Fervaha G, Foussias G, Agid O, Remington G. Motivational deficits in early schizophrenia: prevalent, persistent, and key determinants of functional outcome. *Schizophrenia Research* 2015;166(1-3):9-16. (1200)

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4.1 Introduction

Through advances in our understanding, treatment and management of individuals with schizophrenia, especially in the early course of the illness, it is possible for individuals with schizophrenia to experience recovery in their functioning within the community. Though some individuals experience such positive outcomes (177), it remains that many people with schizophrenia continue to experience poor functional outcomes (162). A host of clinical factors have been identified as potential barriers for individuals to experience their full potential; however, these remain unclear for patients in the earlier stages of the illness, a timeframe that carries great potential to curb prospective functional impairment and associated burden.

Both cognitive impairments and negative symptoms have emerged as key predictors of functional outcome in individuals with chronic schizophrenia (485, 794, 796, 821, 838, 840, 845, 860). In terms of negative symptoms, it is motivational deficits in particular that have been linked to worse community functioning (673, 679, 839, 845, 850, 873, 876), and emerging evidence suggests that negative symptoms and motivational deficits might mediate the association between cognition and community functioning (660, 813, 865, 866).
Both cognitive impairments and negative symptoms are evident in first episode psychosis, where both have also been identified as predictors of outcome (817, 844, 846, 870, 1201). However, whether motivational deficits play such a critical role in earlier stages of schizophrenia is unclear. To this last point, it is known that negative symptom burden present during the initial acute phase is a poor predictor of the presence or severity of these symptoms during more stable periods (1190, 1191). Relatively less is known about whether these features assessed during a more stable period are predictive of concurrent or longitudinal functioning. In a preliminary study with a relatively small sample of early schizophrenia patients, we found that motivational deficits stood as the most robust predictor of concurrent functioning, and that other features of the illness such as positive symptoms or cognition did not offer any predictive power beyond that of amotivation (891). In the present study, we sought to replicate and extend these findings to a larger sample of such patients.

4.2 Methods

4.2.1 Study Design

Data were collected as part of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) schizophrenia study; for which the details of the study design and primary results are reported elsewhere (254, 1202). The CATIE project conducted between January 2001 and December 2004 at 57 sites in the United States was designed to examine the effectiveness of atypical and typical antipsychotic medication for the treatment of persons with schizophrenia. Participants were eligible to participate in the CATIE study if they were between the ages of 18 and 65 years and had a diagnosis of schizophrenia confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (1203). Participants were excluded from the study if they had a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; had a documented history of treatment refractory illness; or had a serious and unstable medical condition. Notably, patients in their first-episode of schizophrenia were excluded. In the CATIE study, participants were considered to be in their first episode if they had experienced psychotic symptoms for less than 3 years or if they first began antipsychotic treatment within the past year. Eligible participants were initially randomized to one of five study medications under double-blind conditions and were followed up to 18 months or until treatment was discontinued for any
reason (1202). Patients who discontinued their initially assigned treatment were eligible to receive other treatments and continue in the trial (1202).

The study was approved by the institutional ethics review board at each site, and written informed consent was obtained from the patients or their legal guardians.

4.2.2 Instruments

The primary measure of interest in the present study was the Heinrichs-Carpenter Quality of Life Scale (QLS) (1197). The QLS is a rater-administered semi-structured interview instrument that assesses functional status. Previous work has found that scores derived through patient interview are not different from ratings made by high-contact clinicians, and that these two scores are significantly correlated for this scale (1204). The scale consists of 21 items rated on a 0 to 6 scale (higher scores reflect better functioning) and is comprised of four subscales: interpersonal relations, instrumental role functioning, intrapsychic foundations, and use of common objects and activities. The scale total score is computed as the mean of all items. Since the items within the intrapsychic foundations subscale are considered measures of negative symptoms (e.g., avolition and anhedonia), they were excluded and the total score was calculated as the mean of the remaining 14 items (1205, 1206). Notably, the QLS is one of the most widely used instruments in schizophrenia research to assess real world functional status (1207), and has been included as an outcome measure in large-scale treatment trials (255, 1208, 1209). In addition to the global score, two individual domains of functioning (social and role) were also examined. Consistent with previous work (821), number of days worked in the past 30 days was also used as an indicator of occupational functioning and productivity; however, because this variable was highly skewed, it was only examined with non-parametric statistical tests.

Motivation was evaluated using the sum of 3 items from the intrapsychic foundations subscale of the QLS: curiosity, goal-directed motivation and sense of purpose (865). These items measure general trait-like motivation, and have been used in numerous empirical studies (765, 865, 866, 871, 879, 1210-1212). All items were significantly inter-correlated (correlation range, 0.47 - 0.68, all p < 0.001), and highly related to the overall motivation score (correlation range, 0.80 - 0.88, all p < 0.001). It is notable that this measure has been shown to have significant overlap
with other measures of amotivation (1211), but conversely has not been linked with severity of positive symptoms (1210), or depressive symptoms (765). Higher scores on this measure reflect a greater level of motivation or, conversely, less deficits.

A secondary measure of amotivation was also employed. Specifically, a social amotivation score was derived by summing the following items from the Positive and Negative Syndrome Scale (PANSS) (474): emotional withdrawal, passive apathetic withdrawal, and active social avoidance (685). These items have been shown to form a separate subfactor within the PANSS negative symptoms factor (683, 685), and represent items that demonstrate the highest convergence with more detailed amotivation measures (693). This measure of social amotivation was significantly correlated with the QLS-derived motivation measure \( r = -0.44, p < 0.001 \). Higher scores on this social amotivation measure reflect greater motivational deficits.

Other measures of interest included the PANSS to assess severity of discrete aspects of psychopathology such as positive and disorganized symptoms (544) and negative symptoms related to diminished expression (685), Calgary Depression Scale for Schizophrenia (CDSS) to assess depressive symptoms (649), Simpson-Angus Scale (SAS) to assess extrapyramidal symptoms (1195, 1213), and the Barnes Akathisia Rating Scale (BARS) to assess akathisia (1194).

Neurocognition was evaluated using a battery of assessments, as described in a previous report (1214), which were converted into standardized scores and combined to construct five domain scores: verbal memory, vigilance, processing speed, reasoning and problem solving, and working memory (661). These domain scores were standardized and averaged to create a neurocognitive composite score which was used in the present analysis.

As previous work has shown that receipt of social (i.e., income) support has an influence on functional outcomes (219), we also included this variable in the present study. Whether patients were receiving Social Security Disability Insurance or Supplemental Security Income was noted.

Participants were evaluated using the aforementioned measures at baseline, and again after 6-months of treatment, thus allowing for the examination of baseline predictors of latter outcome, as well as the assessment of longitudinal inter-relationships.
4.2.3 Selection of Participants

Participants who were between the ages of 18 and 35 years and had received antipsychotic medication for 5 years or less were considered to be in the early phase of illness and included in the present study. It should be underscored that first-episode patients, as defined above, were not included in the present study. Individuals experiencing significant akathisia (BARS global rating greater than 2) and/or prominent extrapyramidal symptoms (any rating of greater than 2 on the SAS) were excluded. Moreover, participants experiencing significant depressive symptoms (CDSS total score greater than 6) were also excluded. These exclusions were enforced to exclude the possibility that motivational deficits assessed were secondary to factors such as akinesia or depressed mood.

4.2.4 Statistical Analysis

Proportions of participants meeting criterion for severe motivational impairments (QLS motivation item rating of \( \leq 1 \), corresponding to severe impairment) or experiencing any degree of motivational deficit (QLS motivation item rating of \( \leq 4 \), corresponding to at least mild-moderate impairment) are reported. Differences in continuous and categorical variables between individuals receiving social support and those who are not were examined using independent-samples t-tests or \( \chi^2 \), respectively.

Bivariate relationships between variables were quantified using Pearson product-moment correlation coefficients, with the exception of analyses with the work productivity measure where Spearman rank-order correlation coefficients were computed. Difference in the magnitude of association between variables was examined using the Steiger test for dependent correlation coefficients. Next, independent predictive power of variables was assessed using multivariate regression models. Last, we examined whether prospective change in motivation and cognitive performance was related to change in functional status over 6 months. A \( P \) value of less than 0.05 (2-sided) was considered statistically significant. Statistical analyses were carried out using SPSS version 20 (IBM Corporation, Armonk, NY).
4.3 Results

4.3.1 Patient Characteristics

Baseline demographic and clinical characteristics of the study sample are presented in Table 4-1. One hundred and sixty-six individuals with minimal extrapyramidal and depressive symptoms had available symptom severity, motivation, functioning, and cognitive data. The mean age of the participants was in the mid-twenties and on average patients had received antipsychotic treatment for less than 3 years. In this sample of early schizophrenia patients, 15.1% experienced severe deficits in motivation and 76.5% had some degree of motivational impairment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (S.D.) or N (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic</td>
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<tr>
<td>Age (years)</td>
<td>25.5 (4.8)</td>
<td>18 - 35</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>137 (82.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Race (white)</td>
<td>110 (66.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Patient’s education (years)</td>
<td>12.1 (2.0)</td>
<td>1 - 18</td>
</tr>
<tr>
<td>Clinical (non-psychopathology)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration since first prescribed antipsychotic medication (years)</td>
<td>2.6 (1.6)</td>
<td>0 - 5</td>
</tr>
<tr>
<td>Antipsychotic type</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Atypical only 112 (67.5%) -
Typical 16 (9.6%) -
None 38 (22.9%) -

**Symptom severity**

Overall severity of psychopathology (PANSS total score) 74.0 (17.4) 34 - 123
Positive symptoms (PANSS factor score) 21.4 (6.7) 8 - 38
Negative symptoms (PANSS factor score) 19.5 (7.1) 7 - 40
Disorganized symptoms (PANSS factor score) 17.0 (5.5) 7 - 34
Excitement and hostility symptoms (PANSS factor score) 6.9 (2.7) 4 - 16
Anxiety and depressive symptoms (PANSS factor score) 9.1 (3.1) 4 - 20
Social amotivation score (PANSS) 9.0 (3.3) 3 - 18
Diminished expression score (PANSS) 10.5 (4.7) 4 - 23
Depressive symptoms (CDSS) 2.2 (2.0) 0 - 6
Motivation score 8.8 (4.2) 0 - 18

**Functional status**

Global functioning (QLS total score excluding the intrapsychic foundations subscale) 2.7 (1.2) 0.4 - 5.9
Social functioning (QLS - interpersonal relations subscale) 2.9 (1.4) 0.0 - 6.0
Role functioning (QLS - instrumental role subscale score) 2.0 (1.8) 0.0 - 6.0
Numbers of days spent in employment in past 30 days 3.2 (6.7) 0 - 24
Employment status (unemployed) 136 (81.9%) -
Receipt of social assistance 67 (40.4%) -

Abbreviations: PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia; QLS: Quality of Life Scale; S.D.: Standard Deviation.

Approximately 40% of early schizophrenia patients were receiving public support; however, these patients did not differ from those not receiving social assistance on level of motivation ($t_{164} = 0.82, p = 0.42$), social functioning ($t_{164} = 0.14, p = 0.89$), role functioning ($t_{164} = 0.32, p = 0.75$), or global outcome ($t_{164} = 0.19, p = 0.85$); moreover, the rate of employment did not differ between these two groups of patients (16.4% of those receiving public support versus 19.2% of those not; $\chi^2 = 0.21, p = 0.65$). Of the participants that were employed, those receiving social support did however earn a significantly lower income relative to individuals not receiving support (mean monthly income of $350 versus $1048, respectively; $t_{26} = 3.61, p = 0.001$).

4.3.2 Predictors of Outcome

Both motivational deficits and cognitive performance were related to concurrent overall functional status (Table 4-2; Figure 4-1); however, motivational deficits demonstrated greater predictive ability than neurocognition ($z = 6.37, p < 0.001$). Moreover, motivational deficits demonstrated a pervasive effect on functioning, impacting each domain of functioning examined, while neurocognition scores did not predict concurrent social functioning or work productivity (Table 4-2). Scores from individual domains of neurocognition, particularly verbal memory, vigilance and working memory were related to concurrent overall functional status, but the
The magnitude of association was similar to that of the neurocognitive composite score (Table 4-6), and the magnitude of association with functional status was significantly less than that of motivation (all p's < 0.001).

Table 4-2. Relationship between clinical variables and measures of functional status

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Global functional outcome</th>
<th>Social functioning</th>
<th>Role functioning</th>
<th>Number of days worked in past 30 days&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motivation</td>
<td>0.69***</td>
<td>0.58***</td>
<td>0.54***</td>
<td>0.23*</td>
</tr>
<tr>
<td>Neurocognition</td>
<td>0.19*</td>
<td>0.10</td>
<td>0.18*</td>
<td>0.06</td>
</tr>
<tr>
<td>Social amotivation</td>
<td>-0.58***</td>
<td>-0.53***</td>
<td>-0.39***</td>
<td>-0.18*</td>
</tr>
</tbody>
</table>

Reported correlations are statistically significant at the *p<0.05 level; or **p<0.01; or ***p<0.001

<sup>a</sup> Spearman's rank-order correlation coefficients
Figure 4-1. Bivariate relationship between (a) motivation and functional outcome, and (b) prospective change in motivation and change in functional status

Examining the independent predictive power of motivation and neurocognition revealed that once motivation was controlled for, cognition did not remain a significant predictor of functional outcome, while motivation continued to demonstrate a robust and significant association (Table 4-3). These findings remained unchanged when examining males and females separately (Table 4-7), or when examining individual cognitive domains rather than the composite neurocognition score (Table 4-8).

Table 4-3. Multivariate regression models with functional status as dependant variables and motivational deficits and neurocognition as predictor variables

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable Added</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Global functional outcome</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Motivation</td>
</tr>
<tr>
<td></td>
<td>Neurocognition</td>
</tr>
<tr>
<td>2</td>
<td><strong>Social functioning</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Motivation</td>
</tr>
<tr>
<td></td>
<td>Neurocognition</td>
</tr>
<tr>
<td>3</td>
<td><strong>Role functioning</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

To explore whether motivational deficits, as compared to other negative symptoms, were particularly related to functional outcome, we entered these two negative symptoms variables simultaneously into a regression model. These analyses demonstrated that motivational deficits were significantly linked to outcome, and that once these deficits were taken into account, negative symptoms related to diminished expression did not offer any independent predictive value (Table 4-4).

Table 4-4. Multivariate regression models with functional status as dependant variables and discrete aspects of negative symptoms as predictor variables

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable Added</th>
<th>$\beta$</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$Global\ functional\ outcome^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation</td>
<td>0.64</td>
<td>10.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Diminished Expression</td>
<td>-0.12</td>
<td>-1.90</td>
<td>0.06</td>
</tr>
</tbody>
</table>

$^a R^2=0.476, F_{2,163}=74.18, p<0.001$

$^b R^2=0.342, F_{2,163}=42.67, p<0.001$

$^c R^2=0.254, F_{2,163}=27.77, p<0.001$
Next, we examined the relationship between motivational deficits and outcome after accounting for selected demographic and clinical variables (Table 4-5). Demographic variables such as age and sex alone explained 3% of the variance in outcome, while positive, disorganized and depressive symptoms explained an additional 17%. After these variables were controlled, neurocognition accounted for an additional 1%. Even after these variables were accounted for, motivational deficits accounted for 30% of the variance in outcome over and above that already explained by the other variables.

Table 4-5. Stepwise multiple regression model predicting global functional outcome

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable Added</th>
<th>β</th>
<th>t-statistic</th>
<th>P-value</th>
<th>R² Change</th>
</tr>
</thead>
</table>

a R²=0.488, F₂,₁₆₃=77.54, p<0.001

b R²=0.348, F₂,₁₆₃=43.59, p<0.001

c R²=0.253, F₂,₁₆₃=27.63, p<0.001
<table>
<thead>
<tr>
<th>1</th>
<th>Age</th>
<th>-0.03</th>
<th>-0.52</th>
<th>0.60</th>
<th>0.030</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
<td>0.04</td>
<td>0.73</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Positive symptoms(^b)</td>
<td>-0.05</td>
<td>-0.71</td>
<td>0.48</td>
<td>0.167</td>
</tr>
<tr>
<td></td>
<td>Disorganized symptoms(^b)</td>
<td>-0.10</td>
<td>-1.40</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>-0.11</td>
<td>-1.94</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Neurocognition</td>
<td>0.003</td>
<td>0.05</td>
<td>0.96</td>
<td>0.006</td>
</tr>
<tr>
<td>4</td>
<td>Motivation</td>
<td>0.63</td>
<td>9.80</td>
<td>&lt;0.001</td>
<td>0.301</td>
</tr>
</tbody>
</table>

\(^a\) Overall Model $R^2=0.504$, $F_{7,158}=22.97$, $p<0.001$.

\(^b\) Calculated using derived factor scores from the Positive and Negative Syndrome Scale.

Note: For ease of presentation, only the regression weights from the final model are shown.

Entering motivation as a predictor first into the models revealed that this variable alone explained 48% of the variance in global functional outcome. We next explored whether any of the variables were significant predictors of outcome, after motivation was accounted for. In this stepwise regression model, the other variables did not demonstrate significant independent predictive ability, suggesting that positive symptoms and cognitive performance are not predictive of outcome over and above the contribution made by motivational impairment.

### 4.3.3 Motivation as a Mediator Variable

That neurocognition demonstrates a bivariate relationship with functioning, which is nullified once motivation is accounted for, suggests that motivation possibly mediates this relationship. We tested this notion using mediation analysis (1215). First, neurocognition was significantly
related to global functional outcome (Table 4-2; $\beta = 0.19$, $p = 0.02$). Second, neurocognition was associated with motivation ($\beta = 0.25$, $p < 0.001$). Motivation was also related to functional outcome (Table 4-2; $\beta = 0.69$, $p < 0.001$). Finally, when both motivational deficits and cognitive performance were used to predict functional outcome, motivation emerged as a significant predictor but cognition did not (Table 4-3). Consistent with this, the Sobel's test was significant ($z = 3.16$, $p = 0.002$), providing evidence that motivation mediated the relationship between cognition and functional outcome in this group of early schizophrenia patients.

### 4.3.4 Longitudinal Functional Outcome

Next, we examined whether motivational deficits and cognitive performance predicted functional outcome after 6 months in a subsample of 105 patients. Notably, participants with follow-up data did not differ from patients for whom follow-up data was not available in terms of severity of psychopathology, motivational deficits, cognition (Table 4-9); however, patients with available follow-up data did have slightly better global functioning at baseline, but this was not the case for the other measures of functional status. The longitudinal analysis was consistent with the baseline cross-sectional findings in that motivation emerged as a significant predictor ($\beta = 0.48$, $p < 0.001$), while neurocognition did not ($\beta = 0.06$, $p = 0.48$; overall model, $F_{2,102} = 17.43$, $p < 0.001$, $R^2 = 0.255$).

After 6 months of treatment, and consistent with the baseline visit, 12.4% of the patients demonstrated severe motivational impairments, with 75.2% demonstrating some degree of motivational impairment. At this follow-up visit, the pattern of cross-sectional relationships between clinical variables and functioning emerged which was similar to that observed at baseline, where motivational deficits were the more robust and reliable predictor of functional status (Table 4-10). Considering motivation and neurocognition together, motivational deficits were a significant independent predictor of concurrent (i.e., cross-sectional) functioning ($\beta = 0.73$, $p < 0.001$), while cognition was not ($\beta = 0.001$, $p = 0.99$; overall model, $F_{2,87} = 48.92$, $p < 0.001$, $R^2 = 0.529$).

Last, we examined whether change in motivation was related to change in overall functioning. Increases in motivation over 6 months were significantly associated with improvements in
functioning ($r = 0.57$, $p < 0.001$; Figure 4-1). Interestingly, changes in neurocognitive performance were also related to improvements in functioning ($r = 0.26$, $p = 0.01$). Examining both of these variables together in a multiple regression model revealed that changes in motivation were independently related to changes in functioning ($\beta = 0.56$, $p < 0.001$), but that once this variable is controlled for, changes in cognitive performance were not related to changes in functional outcome ($\beta = 0.14$, $p = 0.13$; overall model, $F_{2,87} = 25.11$, $p < 0.001$, $R^2 = 0.366$). Controlling for changes in positive and depressive symptoms did not alter these findings; motivation remained a significant predictor of changes in outcome ($\beta = 0.56$, $p < 0.001$), whereas changes in cognition were not ($\beta = 0.12$, $p = 0.18$; overall model, $F_{4,85} = 14.21$, $p < 0.001$, $R^2 = 0.401$). Finally, adjusting for baseline scores by including these variables into the model also did not influence the results. In this model, neither baseline cognitive performance nor prospective change in performance were significant predictors of changes in functional outcome ($p's > 0.10$), whereas baseline functioning and motivation did emerge as a significant predictors ($p's < 0.05$). Even when these scores were accounted for, changes in motivation remained a significant predictor of changes in functional outcome ($\beta = 0.74$, $p = 0.001$; overall model, $F_{5,84} = 20.09$, $p < 0.001$, $R^2 = 0.545$).

### 4.3.5 Control Analyses

As both the motivation and functional status were assessed with the same instrument, the relationships observed between the two variables might reflect to some degree rating bias. To evaluate this, we examined whether motivation had any predictive value for social or role functioning, once a different functioning variable also extracted from the same instrument had been controlled for. If the present findings were simply reflective of a halo effect, we would then expect that motivation would have no predictive value after the variance from another portion of the instrument is accounted for. We did not find evidence for this (Table 4-11), as motivation continued to explain a significant portion of the variance in functional outcome even after the variance ascribed to different aspects of functioning were parsed. Thus, motivational deficits seem to have significant predictive value in determining functional status that cannot be fully accounted for rater bias. Consistent with this, motivation but not cognition was related to work productivity (which was not rated on the same instrument); moreover, changes in motivation
were linked to changes in this measure of functioning \((r = 0.27, p = 0.006)\), whereas changes in cognition were not \((r = 0.10, p = 0.36)\).

Employing a secondary measure of amotivation derived from the PANSS, resulted in a similar pattern of findings. This measure was related to all facets of functioning evaluated (Table 4-2), and examining the independent predictive value of this variable revealed that motivation here too was a significant determinant of global outcome \((\beta = -0.56, p < 0.001)\), while cognition did not emerge as a significant predictor \((\beta = 0.09, p = 0.15; \text{overall model, } F_{5,163} = 41.96, p < 0.001, R^2 = 0.340)\). Examining change scores revealed identical findings; namely, changes in motivation as measured with PANSS were linked to changes in functioning \((\beta = -0.44, p < 0.001)\), whereas changes in cognition were not independently predictive \((\beta = 0.17, p = 0.09; \text{overall model, } F_{5,87} = 15.05, p < 0.001, R^2 = 0.257)\).

### 4.4 Discussion

The present study examined the predictors of concurrent and longitudinal functional outcome in patients with early schizophrenia. We found that motivational deficits stand as the single most robust predictor of functional outcome in early-course patients. That the vast majority of individuals experienced motivational impairment (more than 75%), and that the relationship with outcome was seen so soon in the illness’ course, underscores the need to better understand underlying mechanisms in order to establish effective interventions that will curb longer-term poor functioning. It is important to note that these deficits in motivation cannot be fully ascribed to chronicity effects (e.g., extended institutionalization).

Consistent with previous literature, performance on cognitive tests emerged as a significant predictor of functional outcome \((861)\). However, and consistent with previous reports in more chronic samples \((865, 866, 871)\), we find that this association is fully mediated by motivational impairment, and that motivational deficits are more closely linked with functioning than cognition. Once motivational impairments are considered, cognition does not seem to offer any additional predictive value for the determination of global community functioning, or individual domains of functioning such as social and vocational. This finding does not serve to diminish the importance of cognition in terms of its relationship to functional status; rather, it highlights that
there is overlap in the variance in functional outcome explained by neurocognition and amotivation, and that the relationship between cognition and real-world outcomes is largely indirect, mediated by other variables such as motivation.

Changes in both motivation and cognitive performance were each linked to changes in functional status over time, a finding that is in keeping with one previous report on patients with chronic schizophrenia (765). Like the analyses with concurrent functional status, changes in functioning were more closely linked to changes in motivation, and once these were accounted for changes in cognitive performance did not hold significant independent predictive value. This highlights the fact that motivational deficits are inextricably linked with functional outcome even in the early stages of schizophrenia, underscoring the need to assess and treat these impairments from the illness’ outset.

The relationship between cognition and functioning was found to be mediated by deficits in motivation. The mechanisms underlying these inter-relationships remain to be discerned; however, we can speculate as to possible explanations. One possibility is that core cognitive impairment undermines goal-directed motivation, which ultimately leads to poor functioning. For example, impairments in basic cognitive processing (e.g., the ability to hold and manipulate information) may hinder patients' ability to efficiently form and execute plans. Alternatively, it is possible that general motivation impacts cognitive test performance through participants putting forth suboptimal effort during the testing procedures, and it is in fact this motivational influence on cognitive performance that is linked to outcome; once this is controlled for, the relationship between cognitive performance and functioning is nullified. There is some evidence that test-taking motivation is related to cognitive test performance (1131, 1216). However, it remains a task for future work to evaluate each of these domains, if possible, independent of one another, as well as their predictive value for the determination of functional outcome. These theoretical points aside, the present results clearly demonstrate that motivational deficits as a predictive variable hold value in determining outcome.

Positive symptoms did not explain functional outcome, over and above the contribution made by motivational deficits, although they did explain a portion of the variance when motivation was not accounted for. This is in keeping with our previous report involving patients early in the illness (891). This lack of relationship may at least in part be due to the fact that these individuals
have been treated for these symptoms (for an average of less than 3 years); thus, our conclusions around the role of positive symptoms cannot be generalized to more acutely ill patients, but do emphasize that clinical features other than positive psychotic symptoms play an important role in determining outcome in stable patients.

In our multivariate regression model (Table 11-5), psychopathology variables together explained 16.7% of the variance of functional outcome, when entered before cognition and motivation. These variables however did not offer significant independent predictive value once motivational deficits were considered. That is to say that variables such as depressive symptoms did not contribute to the determination of functioning over and above the contribution made by motivational deficits, though a trend-level association was discerned. This is in contrast to some previous work that has highlighted the impact of depressive symptoms on functional status independent of negative symptoms (794, 796, 851, 869, 876); however, other investigations have also failed to find a significant independent effect of depression (840, 845, 850). Our failure to find a significant association between depression and outcomes in the present sample may be related in part to the fact that we excluded patients with moderate-severe depressive symptoms. To explore this possibility we re-ran the multivariate regression model including individuals with more severe depressive symptoms, and the results were similar to our original model in terms of amount of explained variance by each successive block of variables and the robust effect of motivational deficits; however, the predictive value of depressive symptoms was statistically significant (Table 4-12), but the effect size was similarly small to our original model (Table 4-5).

In our previous study with early schizophrenia patients, we did not find a significant association between depression and outcome, which may have been related to the exclusion of patients with mood disorders or the relatively low power to detect smaller relationships (891).

Social assistance has been found to be linked to poorer functional outcomes in patients with chronic schizophrenia (219, 845). We did not find a similar relationship in the present sample of early-course patients, suggesting that these support systems may not serve as an disincentive to real-world functioning in individuals with a recent onset of illness. This is consistent with previous work with first-episode patients demonstrating that these relatively younger patients consider adequate functioning within the community an important life goal (1217).
The present investigation had several strengths including the relatively large sample of patients evaluated, a longitudinal follow-up allowing for the examination of change scores, and the inclusion of a motivation measure that evaluates this construct from both a subjective and objective viewpoint. Nonetheless, there are limitations warranting comment. First, the present study did not include measures of social cognition, so it remains possible that this variable may have predictive value in the determination of outcome beyond that of motivation. As an exploratory analysis, we examined the predictive value of an emotion processing test (661, 1218), and measures of outcome (Table 4-6). This social cognition measure was only weakly, and inconsistently, related to measures of outcome, similar to findings observed with neurocognition. This finding should be viewed in light of the poor psychometric properties of this social cognition test (661), and the lack of tests evaluating other facets of social cognition (e.g., theory of mind). Second, baseline scores were obtained from individuals potentially changing medications; however, similar cross-sectional relationship emerged after 6 months of treatment. Third, the magnitude of mean change in the variables examined has been cited to be minimal (1208, 1219, 1220), so the pattern of longitudinal changes observed here should be confirmed in patients who as a group demonstrate more substantial changes. It should be mentioned that although a substantial mean change was not observed, there was considerable variance in the change scores meaning that at least some individuals evidenced marked changes (Table 4-13), and the relationships reported herein are exploiting this variation. Nonetheless, the lack of substantial changes after 6 months serves to highlight the persistent nature and the lack of effective treatments for these deficits. Fourth, we employed a derived measure of motivation rather than a standalone instrument. Future work should examine motivational deficits using laboratory tests, and examine the predictive value of performance-based measures of motivation in determining real-world functioning. There is some evidence that motivational deficits evaluated in this manner are also predictive of functional status (1221-1223). Last, the present study examined only selected predictor variables based on the burgeoning literature on the importance of cognition and negative symptoms in predicting functioning in patients with schizophrenia. Moving forward, it would be valuable to delineate other variables that might mediate the relationship between motivational impairment and functioning, as such variables may represent viable targets for treatment intervention.
Despite advances in our understanding of schizophrenia, outcomes remain poor for many people with this illness. Our investigation reinforces the notion that motivational deficits stand as one of the most important barriers to functional recovery in patients with schizophrenia, even early in the illness’ course. It should be highlighted that these symptoms are prevalent in the early stages of schizophrenia and even following treatment. A more detailed understanding of the multifaceted nature of motivational deficits (881, 882) is critical to therapeutic developments given the importance they seem to play in functioning. Further to this point, though motivational deficits were linked to outcome, future investigations need to delineate the mechanisms underlying these deficits. It may be the case that patients experience these deficits via different (neurobiological) mechanisms (e.g., some linked with abnormal computations of effort demands versus others due to aberrant learning about rewards in the environment, or indeed a combination of factors) (881, 884), with clarification of these providing the opportunity to personalize treatment.

### 4.5 Additional Tables

Table 4-6. Relationship between individual domains of cognition and functioning at baseline

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Global Functional outcome</th>
<th>Social functioning</th>
<th>Role functioning</th>
<th>Number of days worked in past 30 daysa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>0.16*</td>
<td>0.09</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Vigilance</td>
<td>0.19*</td>
<td>0.14</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.12</td>
<td>0.05</td>
<td>0.13</td>
<td>-0.04</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.03</td>
<td>-0.03</td>
<td>0.04</td>
<td>-0.01</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.17*</td>
<td>0.10</td>
<td>0.15</td>
<td>0.07</td>
</tr>
<tr>
<td>Sex</td>
<td>Model</td>
<td>Variable Added</td>
<td>β</td>
<td>t-statistic</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>---------------------</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>Males</td>
<td>1</td>
<td><em>Global functional outcome</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motivation</td>
<td>0.71</td>
<td>11.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurocognition</td>
<td>-0.03</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td><em>Social functioning</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motivation</td>
<td>0.62</td>
<td>8.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurocognition</td>
<td>-0.09</td>
<td>-1.19</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td><em>Role functioning</em>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Motivation</td>
<td>0.48</td>
<td>6.14</td>
</tr>
</tbody>
</table>

Reported correlations are statistically significant at the *p<0.05* level; or **p<0.01; or ***p<0.001

<sup>a</sup> Spearman's rank-order correlation coefficients

<sup>b</sup> Evaluated using a single test - the Facial Emotion Discrimination Task (FEDT)
**Females**

1. *Global functional outcome*<sup>d</sup>

<table>
<thead>
<tr>
<th></th>
<th>Motivation</th>
<th>Neurocognition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.54</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>3.46</td>
<td>1.65</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td>0.11</td>
</tr>
</tbody>
</table>

2. *Social functioning*<sup>e</sup>

<table>
<thead>
<tr>
<th></th>
<th>Motivation</th>
<th>Neurocognition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.41</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>2.33</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>0.38</td>
</tr>
</tbody>
</table>

3. *Role functioning*<sup>f</sup>

<table>
<thead>
<tr>
<th></th>
<th>Motivation</th>
<th>Neurocognition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.49</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>3.17</td>
<td>2.00</td>
</tr>
<tr>
<td></td>
<td>0.004</td>
<td>0.06</td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Overall Model $R^2=0.492$, $F_{2,134}=64.86$, $p<0.001$.

<sup>b</sup> Overall Model $R^2=0.363$, $F_{2,134}=32.22$, $p<0.001$.

<sup>c</sup> Overall Model $R^2=0.232$, $F_{2,134}=20.29$, $p<0.001$.

<sup>d</sup> Overall Model $R^2=0.386$, $F_{2,26}=8.17$, $p=0.002$.

<sup>e</sup> Overall Model $R^2=0.208$, $F_{2,26}=3.41$, $p=0.048$.

<sup>f</sup> Overall Model $R^2=0.379$, $F_{2,26}=7.93$, $p=0.002$. 
Table 4-8. Multivariate regression models predicting global functional outcome with motivation and individual domains of cognition as predictors

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Model</th>
<th>Variable Added</th>
<th>$\beta$</th>
<th>$t$-statistic</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Global functional outcome</em></td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Motivation</td>
<td>0.70</td>
<td>11.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verbal memory</td>
<td>-0.02</td>
<td>-0.38</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Motivation</td>
<td>0.69</td>
<td>11.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vigilance</td>
<td>0.05</td>
<td>0.89</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Motivation</td>
<td>0.70</td>
<td>12.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Processing speed</td>
<td>-0.04</td>
<td>-0.60</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Motivation</td>
<td>0.69</td>
<td>12.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reasoning</td>
<td>-0.02</td>
<td>-0.40</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Motivation</td>
<td>0.68</td>
<td>11.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Working memory</td>
<td>0.09</td>
<td>1.49</td>
<td>0.14</td>
</tr>
<tr>
<td><em>Social functioning</em></td>
<td>1&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Motivation</td>
<td>0.60</td>
<td>9.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal memory</strong></td>
<td>-0.07</td>
<td>-1.04</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motivation</strong></td>
<td>0.59</td>
<td>9.02</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vigilance</strong></td>
<td>0.02</td>
<td>0.32</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td>-0.08</td>
<td>-1.29</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reasoning</strong></td>
<td>-0.07</td>
<td>-1.14</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td>0.03</td>
<td>0.47</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Role functioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Motivation</strong></td>
<td>0.50</td>
<td>7.13</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Verbal memory</strong></td>
<td>0.01</td>
<td>0.09</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vigilance</strong></td>
<td>0.07</td>
<td>0.94</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation</td>
<td>0.50</td>
<td>7.17</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Processing speed</td>
<td>0.008</td>
<td>0.12</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation</td>
<td>0.50</td>
<td>7.37</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reasoning</td>
<td>0.01</td>
<td>0.18</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation</td>
<td>0.49</td>
<td>7.20</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Working memory</td>
<td>0.10</td>
<td>1.49</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

\[ a \, R^2=0.477, \, F_{2,163}=74.21, \, p<0.001 \]
\[ b \, R^2=0.492, \, F_{2,163}=75.12, \, p<0.001 \]
\[ c \, R^2=0.477, \, F_{2,163}=74.42, \, p<0.001 \]
\[ d \, R^2=0.477, \, F_{2,163}=74.23, \, p<0.001 \]
\[ e \, R^2=0.483, \, F_{2,163}=79.20, \, p<0.001 \]
\[ f \, R^2=0.344, \, F_{2,163}=42.82, \, p<0.001 \]
\[ g \, R^2=0.357, \, F_{2,163}=43.07, \, p<0.001 \]
\[ h \, R^2=0.347, \, F_{2,163}=43.25, \, p<0.001 \]
\[ i \, R^2=0.345, \, F_{2,163}=42.99, \, p<0.001 \]
\[ j \, R^2=0.341, \, F_{2,163}=42.17, \, p<0.001 \]
\[ k \, R^2=0.251, \, F_{2,163}=27.34, \, p<0.001 \]
\[^1\] R^2=0.262, F_{2,163}=27.54, p<0.001

\[^m\] R^2=0.251, F_{2,163}=27.34, p<0.001

\[^n\] R^2=0.251, F_{2,163}=27.36, p<0.001

\[^o\] R^2=0.261, F_{2,163}=28.81, p<0.001

Table 4-9. Baseline demographic and clinical characteristics for study sample stratified by availability of follow-up data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with follow-up data available (N=105)</th>
<th>Patients with follow-up data not available (N=61)</th>
<th>P-value comparing groups</th>
<th>t-test or (\chi^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>25.4 (4.9)</td>
<td>25.7 (4.7)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Sex (males)</td>
<td>85 (81.052%)</td>
<td>52 (85.2%)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Race (white)</td>
<td>70 (66.7%)</td>
<td>40 (65.6%)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Patient’s education (years)</td>
<td>12.2 (1.7)</td>
<td>11.9 (2.4)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical (non-psychopathology)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration since first prescribed antipsychotic medication (years)</td>
<td>2.5 (1.7)</td>
<td>2.9 (1.5)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Antipsychotic type</td>
<td></td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Category</td>
<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Atypical only</td>
<td>73 (69.5%)</td>
<td>39 (63.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>9 (8.6%)</td>
<td>7 (11.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23 (21.9%)</td>
<td>15 (24.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Symptom severity**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall severity of psychopathology (PANSS total score)</td>
<td>72.1 (17.0)</td>
<td>77.2 (17.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Positive symptoms (PANSS factor score)</td>
<td>20.8 (6.3)</td>
<td>22.5 (7.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Negative symptoms (PANSS factor score)</td>
<td>19.2 (7.0)</td>
<td>20.0 (7.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Disorganized symptoms (PANSS factor score)</td>
<td>16.6 (5.3)</td>
<td>17.7 (5.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Excitement and hostility symptoms (PANSS factor score)</td>
<td>6.5 (2.5)</td>
<td>7.7 (2.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>Anxiety and depressive symptoms (PANSS factor score)</td>
<td>9.0 (3.1)</td>
<td>9.2 (3.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Social amotivation score (PANSS)</td>
<td>8.8 (3.3)</td>
<td>9.4 (3.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diminished expression score (PANSS)</td>
<td>10.4 (4.4)</td>
<td>10.7 (5.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Depressive symptoms (CDSS)</td>
<td>2.2 (2.0)</td>
<td>2.1 (2.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Motivation score</td>
<td>9.2 (4.2)</td>
<td>8.3 (4.3)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
### Cognition

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) Case</th>
<th>Mean (SD) Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global neurocognition</td>
<td>0.4 (0.8)</td>
<td>0.4 (0.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>0.2 (0.9)</td>
<td>0.2 (1.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Vigilance</td>
<td>0.2 (1.0)</td>
<td>0.2 (0.9)</td>
<td>0.93</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.3 (0.8)</td>
<td>0.5 (1.0)</td>
<td>0.22</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.5 (0.7)</td>
<td>0.4 (0.9)</td>
<td>0.68</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.3 (0.9)</td>
<td>0.3 (0.8)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

### Functional status

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD) Case</th>
<th>Mean (SD) Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global functioning (QLS total score excluding the intrapsychic foundations subscale)</td>
<td>2.9 (1.2)</td>
<td>2.5 (1.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Social functioning (QLS - interpersonal relations subscale score)</td>
<td>3.0 (1.4)</td>
<td>2.6 (1.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Role functioning (QLS - instrumental role subscale score)</td>
<td>2.2 (1.8)</td>
<td>1.7 (1.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Numbers of days spent in employment in past 30 days</td>
<td>2.9 (6.2)</td>
<td>3.8 (7.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>Employment status (unemployed)</td>
<td>86 (81.9%)</td>
<td>50 (82.0%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Receipt of social assistance</td>
<td>37 (35.2%)</td>
<td>30 (49.2%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Abbreviations: PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia; QLS: Quality of Life Scale; S.D.: Standard Deviation.

Table 4-10. Relationship between clinical variables and functioning at the follow-up visit

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Global functional outcome</th>
<th>Social functioning</th>
<th>Role functioning</th>
<th>Number of days worked in past 30 days$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motivation</td>
<td>0.75***</td>
<td>0.59***</td>
<td>0.74***</td>
<td>0.45***</td>
</tr>
<tr>
<td>Neurocognition</td>
<td>0.32**</td>
<td>0.25*</td>
<td>0.29**</td>
<td>0.19</td>
</tr>
<tr>
<td>Social amotivation</td>
<td>-0.51***</td>
<td>-0.52***</td>
<td>-0.30**</td>
<td>-0.14</td>
</tr>
<tr>
<td>Social cognition$^a,b$</td>
<td>0.11</td>
<td>0.14</td>
<td>0.04</td>
<td>-0.03</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>0.33**</td>
<td>0.30**</td>
<td>0.25*</td>
<td>0.13</td>
</tr>
<tr>
<td>Vigilance</td>
<td>0.28**</td>
<td>0.23*</td>
<td>0.27*</td>
<td>0.23*</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.22*</td>
<td>0.14</td>
<td>0.24*</td>
<td>0.15</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.22*</td>
<td>0.18</td>
<td>0.16</td>
<td>0.09</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.13</td>
<td>0.08</td>
<td>0.11</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Reported correlations are statistically significant at the *p<0.05 level; or **p<0.01; or ***p<0.001

$^a$ Spearman's rank-order correlation coefficients

$^b$ Evaluated using a single test - the Facial Emotion Discrimination Task (FEDT)
Table 4-11. Relationship between specific aspects of functional status and motivational deficits independent of functioning within a different psychosocial domain

<table>
<thead>
<tr>
<th>Model</th>
<th>Step</th>
<th>Variable Added</th>
<th>$\beta$</th>
<th>$t$-statistic</th>
<th>$P$-value</th>
<th>$R^2$ Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Social functioning$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Role functioning</td>
<td>0.09</td>
<td>1.28</td>
<td>0.20</td>
<td>0.131</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Motivation</td>
<td>0.54</td>
<td>7.33</td>
<td>&lt;0.001</td>
<td>0.215</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Role functioning$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Social functioning</td>
<td>0.11</td>
<td>1.28</td>
<td>0.20</td>
<td>0.131</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Motivation</td>
<td>0.44</td>
<td>5.29</td>
<td>&lt;0.001</td>
<td>0.127</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Change in social functi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Change in role functi</td>
<td>0.04</td>
<td>0.40</td>
<td>0.69</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Change in motivation</td>
<td>0.40</td>
<td>3.90</td>
<td>&lt;0.001</td>
<td>0.123</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Change in role functio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Change in social functi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Change in motivation</td>
<td>0.45</td>
<td>4.65</td>
<td>&lt;0.001</td>
<td>0.166</td>
</tr>
</tbody>
</table>

$^a$ Overall Model $R^2=0.347$, $F_{2,163}=43.25$, $p<0.001$.

$^b$ Overall Model $R^2=0.259$, $F_{2,163}=28.43$, $p<0.001$. 
Overall Model $R^2=0.174$, $F_{2,102}=10.73$, $p<0.001$.

Overall Model $R^2=0.217$, $F_{2,102}=14.10$, $p<0.001$.

Table 4-12. Multivariate regression model examining the predictive value of sociodemographic and selected clinical variables for functional outcome in 242 patients with early schizophrenia$^a$

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable Added$^b$</th>
<th>$\beta$</th>
<th>$t$-statistic</th>
<th>$P$-value</th>
<th>$R^2$ Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
<td>0.00</td>
<td>-0.01</td>
<td>1.00</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.04</td>
<td>0.90</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Positive symptoms$^c$</td>
<td>-0.05</td>
<td>-0.97</td>
<td>0.33</td>
<td>0.189</td>
</tr>
<tr>
<td></td>
<td>Disorganized symptoms$^c$</td>
<td>-0.11</td>
<td>-1.91</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>-0.13</td>
<td>-2.67</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Neurocognition</td>
<td>-0.006</td>
<td>-0.12</td>
<td>0.91</td>
<td>0.011</td>
</tr>
<tr>
<td>4</td>
<td>Motivation</td>
<td>0.59</td>
<td>10.98</td>
<td>$&lt;0.001$</td>
<td>0.267</td>
</tr>
</tbody>
</table>

$^a$ All patients between the ages of 18 and 35 years and within 5 years of initiating antipsychotic treatment were included; patients with marked depression, extrapyramidal symptoms and/or akathisia were not excluded.

$^b$ Overall Model $R^2=0.482$, $F_{7,234}=31.09$, $p<0.001$.

$^c$ Calculated using derived factor scores from the Positive and Negative Syndrome Scale.

Note: For ease of presentation, only the regression weights from the final model are shown.
## Table 4-13. Change in clinical variables over 6 months

<table>
<thead>
<tr>
<th>Clinical variable (change scores)</th>
<th>Estimated mean difference</th>
<th>SD</th>
<th>Paired-samples t-statistic</th>
<th>P-value</th>
<th>Range</th>
<th>Proportion of individuals with high change scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motivation</td>
<td>0.03</td>
<td>4.37</td>
<td>0.07</td>
<td>0.95</td>
<td>-10 to 16</td>
<td>Change ±3 points: 32.4%</td>
</tr>
<tr>
<td>Neurocognition</td>
<td>0.28</td>
<td>0.58</td>
<td>4.60</td>
<td>&lt;0.001</td>
<td>-1.16 to 1.60</td>
<td>Change ±0.5 points: 45.5%</td>
</tr>
<tr>
<td>Functioning</td>
<td>0.20</td>
<td>1.06</td>
<td>1.91</td>
<td>0.06</td>
<td>-2.48 to 3.00</td>
<td>Change ±1 point: 33.3%</td>
</tr>
</tbody>
</table>
Chapter 5

5 Measuring Motivation in People with Schizophrenia


5.1 Introduction

Motivational deficits are a prevalent feature of schizophrenia, even in the early stages of illness (1200, 1225). The importance of these symptoms is highlighted by consistent findings from several studies demonstrating that these impairments represent a critical link to the poor functional outcomes characterizing this illness (839, 850, 873, 874, 876, 891, 1200). While several instruments exist to evaluate these symptoms, the degree of convergence between scores derived from different instruments, as well as whether motivational deficits scores overlap with ratings of symptom severity in other domains of illness (e.g., depression), is not clear.

Several ratings scales exist that evaluate negative symptoms more broadly and in doing so also tap into aspects of motivational impairment (469). An example of such an instrument includes the Scale for the Assessment of Negative Symptoms (SANS) which includes an avolition/apathy subscale (524). In addition to the SANS, newer negative symptom rating scales have been developed that include specific items tapping into motivational deficits (572, 573). In contrast, some investigators have utilized a motivational deficit specific instrument such as the Apathy Evaluation Scale (AES) in order to assess the severity of this domain of illness (692).

Several studies have supported the notion that motivational deficits evaluated using different ratings scales provide converging information. For example, a previous study using the newer
Clinical Assessment Interview for Negative Symptoms has found moderate overlap between motivational deficit ratings derived from this scale and those derived from the SANS (573). Another study reported a high degree of overlap between motivational deficits evaluated using another new rating scale, the Brief Negative Symptom Scale, and scores derived from the AES (1226). Motivational deficits, as rated on the SANS, have also been linked to scores from other measures of amotivation/apathy (694). Furthermore, in a recent study we showed that ratings of motivational deficits taken from 3 different ratings scales all provided convergent information, and factor analysis revealed a single-factor solution, suggesting that ratings from these different scales were all tapping into a similar unifying construct (i.e., motivational deficits) (1227).

In the present study we specifically examined the degree of convergence between motivational deficit scores derived from selected instruments, and further explored the discriminant validity of these scores. We hypothesized that motivational deficit scores from different instruments would be highly correlated, and would similarly not be highly related to other variables such as positive and depressive symptom severity.

5.2 Methods

5.2.1 Participants

Patients with schizophrenia were recruited from outpatient clinics at the Centre for Addiction and Mental Health. Selection criteria for participants included: (1) diagnosis of a schizophrenia or schizoaffective disorder depressed subtype (no current mood episode), and an absence of any other current Axis I disorder (e.g., substance dependence within the past 3 months), confirmed using the Mini International Neuropsychiatric Interview (1193) and medical records, (2) age 18-35 years, (3) stable outpatient, with no inpatient hospitalizations within the previous 3 months, (4) competence to provide informed consent, evaluated using the MacArthur Competence Assessment Tool (1228), (5) no serious or unstable medical condition, and (6) ability to communicate in English. The study was approved by the institutional research ethics board, and all participants provided written informed consent prior to study participation.
5.2.2 Measures and Procedure

Three instruments were used to evaluate motivational deficits: the clinician version of the AES (692), the Quality of Life Scale (QLS) (1197), and the SANS (524).

The AES is an 18-item rating scale that taps into both subjective and behavioural aspects of motivational deficits. An example item includes: “S/he has motivation.” The total score from the instrument was used as a measure of motivational deficits, where higher scores reflect greater deficits.

From the QLS, we extracted the motivation item as a measure of motivational deficits. This item taps into goal-directed motivation and is rated based on subjective accounts of initiative, persistence, and self-reported achievements. We have previously shown that this item is highly associated with the 3-item intrinsic motivation score also derived from the QLS (865, 1200). Higher scores on this measure reflect greater motivation or, conversely, less motivational deficits.

In addition to scores from the AES and QLS, we also extracted 2 scores from the SANS. Specifically, we used the avolition/apathy subscale global item as a measure of motivational deficits, and in addition we computed another score by summing individual items from the avolition/apathy subscale excluding the global item. In addition to this, we also computed a third score by summing individual items from the avolition/apathy and anhedonia/asociality subscales (excluding global items). For each of these scores higher values indicate greater severity of motivational deficits.

Positive symptom severity was also evaluated using the thought disturbance factor (1229) derived from the anchored version of the Brief Psychiatric Rating Scale (BPRS) (1230). Symptoms of disorganization were also evaluated using factor scores derived from the BPRS (1229, 1230). Severity of depressive symptoms was evaluated using the total score from the Calgary Depression Scale for Schizophrenia (CDSS) (650). Notably, the CDSS does not evaluate symptoms such as anergia, anhedonia, or lack of interest and therefore may represent an instrument that is well suited to discriminate depressive and negative symptoms in schizophrenia. Finally, antipsychotic dosage equivalents were computed using chlorpromazine equivalents (1231).
5.2.3 Statistical Analyses

Convergent and discriminant validity of the motivational deficit scores was evaluated using Spearman’s rank-order correlation coefficients. Next, we wanted to replicate our previous findings of a single-factor solution parsimoniously explaining the data (1227). For this, we conducted an exploratory factor analysis with principal axis extraction on 4 motivation scores (not including the SANS avolition/apathy subscale score). Initially, no rotation was specified; however, the results remain unchanged if varimax or promax rotations were specified. Statistical tests were considered significant at a p-value of less than 0.05 (two-tailed). Data were analyzed using SPSS Statistics version 20 (IMB Corp., Armonk, NY, USA).

5.3 Results

5.3.1 Patient Characteristics

Sixty-two patients with schizophrenia participated in the present study. Sociodemographic and clinical characteristics of the sample are presented in Table 5-1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.) or %</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26.3 (3.9)</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>67.7</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td>Schizophrenia 95.2</td>
</tr>
</tbody>
</table>
Schizoaffective disorder 4.8

Antipsychotic dosage (chlorpromazine) equivalents\(^a\) 530.9 (225.5)

AES Total 37.6 (9.6)

QLS Motivation 3.6 (1.6)

SANS Avolition Global 2.1 (1.3)

SANS Avolition Subscale 5.3 (3.5)

SANS Avolition-Anhedonia Subscales 11.5 (6.7)

BPRS Positive Symptoms 8.1 (4.3)

BPRS Disorganization Symptoms 5.0 (1.8)

CDSS Total 1.8 (2.7)

Abbreviations: AES: Apathy Evaluation Scale; QLS: Quality of Life Scale; SANS: Scale for the Assessment of Negative Symptoms; BPRS: Brief Psychiatric Rating Scale; CDSS: Calgary Depression Scale for Schizophrenia.

\(^a\) 60 patients were receiving atypical antipsychotic monotherapy, while 2 participants were receiving typical antipsychotics.

5.3.2 Convergent Validity

All of the motivational deficit scores were highly inter-correlated (Table 5-2). The factor analysis resulted in a Kaiser–Meyer–Olkin measure of sampling adequacy of 0.79 and a significant Bartlett’s test of sphericity (\(\chi^2 = 162.0, p < 0.001\)). In addition, all communalities were high (i.e., greater than 0.60). Examination of the scree plot and eigenvalues revealed a clear one-factor
solution explaining 71.1% of the variance. Notably, all 4 scores loaded highly onto this factor with loading values each greater than 0.77.

**Table 5-2. Convergent validity between motivation scores**

Table 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AES Total</th>
<th>QLS Motivation</th>
<th>SANS Avolition Global</th>
<th>SANS Avolition Subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES Total</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QLS Motivation</td>
<td>-0.79***</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SANS Avolition Global</td>
<td>0.65***</td>
<td>-0.76***</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>SANS Avolition Subscale</td>
<td>0.68***</td>
<td>-0.74***</td>
<td>0.93***</td>
<td></td>
</tr>
<tr>
<td>SANS Avolition-Anhedonia Subscales</td>
<td>0.68***</td>
<td>-0.70***</td>
<td>0.78***</td>
<td>0.82***</td>
</tr>
</tbody>
</table>

***All correlations are significant at p < 0.001

5.3.3 **Discriminant Validity**

None of the motivational deficit scores were related to positive symptom severity, severity of disorganization, or with the dosage of antipsychotic received (Table 5-3). Motivational deficits scores on the AES were weakly related to severity of depression; this relationship with depression scores was similarly modest for the other motivational deficit scores, but was not statistically significant (Table 5-3).
Table 5-3. Discriminant validity between motivation scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>AES Total</th>
<th>QLS Motivation</th>
<th>SANS Avolition Global</th>
<th>SANS Avolition Subscale</th>
<th>SANS Avolition-Anhedonia Subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive symptoms</td>
<td>-0.02</td>
<td>-0.02</td>
<td>0.09</td>
<td>0.03</td>
<td>0.08</td>
</tr>
<tr>
<td>Disorganization symptoms</td>
<td>0.02</td>
<td>-0.12</td>
<td>0.17</td>
<td>0.12</td>
<td>0.16</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.28*</td>
<td>-0.21</td>
<td>0.12</td>
<td>0.20</td>
<td>0.21</td>
</tr>
<tr>
<td>Antipsychotic dosage</td>
<td>0.02</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.06</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

* Correlations are significant at p < 0.05

5.4 Discussion

The present study sought to examine the overlap in motivational deficit scores across 5 different measures, and further evaluate the relative independence of these scores from other aspects of psychopathology. We found evidence for convergent validity of the 5 scores, suggesting that each of the scores is tapping into a similar underlying construct (i.e., motivational deficits). Furthermore, with the exception of the relationship between the AES and depressive symptoms, all measures of motivation were not associated with severity of positive, disorganization, or depressive symptoms.

One previous study has reported a relationship between the 3-item measure of intrinsic motivation derived from the QLS and SANS avolition scores (1211). Our findings extend this work to demonstrate that even the single QLS motivation item can capture meaningful variance in motivational deficits as compared to more detailed assessments. Our results therefore
highlight the convergent and discriminant validity of the QLS motivation score and suggest that it is a valid measure of motivational deficits in patients with schizophrenia.

It is interesting to note the degree of convergence between the selected measures of motivational deficits, especially given the divergence in item content. For example, the SANS items are scored largely based on behavioural output, whereas the QLS motivation score is based largely on subjective accounts. The AES includes items that evaluate both subjective evaluations of motivation and outward behavioural output. The high correlations observed between the scales might suggest that at least in stable outpatients behavioural output is a reasonable proxy for internal drive.

The measures included all evaluated a general state of motivation, as opposed to motivation for some specific task. Previous work has shown that these two constructs are not necessarily interchangeable (1212); therefore, our findings are only applicable to motivational deficits in general. It should also be noted that we did not include an exhaustive list of motivation measures so the generalizability of the findings to all instruments evaluating motivation and deficits therein remains to be demonstrated empirically. Notwithstanding these points, our findings do demonstrate a high degree of convergence between different measures of motivation, suggesting that they are tapping into a similar underlying construct and can therefore, to some degree, be used interchangeably. The QLS motivation item and the SANS avolition global item are attractive measures of motivation given their convergent and discriminant validity, in addition to anchors that clearly demarcate severity levels.
Chapter 6

6 Incentive Motivation Deficits in Schizophrenia Reflect Effort Computation Impairments During Cost-Benefit Decision Making


6.1 Introduction

Amotivation, or apathy, is a well-documented clinical feature of schizophrenia (SCZ) and a key determinant of longitudinal functioning (875, 876). It has even been argued that amotivation is at the core of the schizophrenic syndrome (454). Consistent with these clinical observations are behavioural findings of reduced goal-directed behaviour based on observed movement (892, 893). However, studies employing objective task-based assessments of these deficits in individuals with SCZ are scarce in the literature.

In the behavioural neuroscience literature, motivation is typically evaluated by measuring the amount of effort an organism expends for a given reward (908). Working within such a framework, pre-clinical studies have implicated a neural network subserving the computation of effort costs that involves the mesolimbic dopaminergic system (908) and the anterior cingulate cortex (986, 989). Specifically, increases in dopaminergic transmission are associated with increases in motivated behaviour (e.g. greater number of lever presses for a given reward) (974), whereas disruption of dopaminergic functioning, through focal lesions or pharmacologically
induced receptor antagonism/depletion, reduces motivated behaviour (906, 959). There is also
evidence that pharmacological manipulations of the dopaminergic system in healthy human
subjects affects motivation (1008). Moreover, and consistent with the pre-clinical literature,
activity within the human anterior cingulate cortex tracks decisions to expend effort (1020,
1022). Given that functioning within these neural regions have been previously shown to be
abnormal in SCZ (365, 761, 1059), such neural dysfunctions may translate to altered
computations of effort cost and, therefore, bias cost-benefit decision-making. Impairment of this
sort would surface behaviourally as a reduction in motivated behaviour, and clinically as apathy.

It is of note that multiple deficits have been found under the umbrella constructs of reward and
motivation processing in SCZ (882). These include deficits in reward learning (1050), neural
responses to reward (1064), and value representations (1071), to name a few. All of these inter-
related, yet distinct, processes can theoretically undermine motivated behaviour. As a result,
assessment of incentive motivation, or the willingness to expend effort for a reward, remains
elusive. In the present study, we sought to behaviourally demonstrate incentive motivation
deficits in SCZ, while accounting for other reward-related variables. We hypothesized that
individuals with SCZ would demonstrate deficits in their willingness to expend effort for reward,
which would not be accounted for by reward learning capacity or valuation of the reward,
consistent with the notion of impairment in the computation of effort cost.

6.2 Methods

6.2.1 Participants

Sixteen outpatients with SCZ and sixteen demographically matched healthy control subjects
(HC) participated in the present study. All patients were tested while on a stable dose of
antipsychotic medication, with no changes for at least 4 weeks. Patients were relatively early in
their disease course (age between 18-35 years) and had a DSM-IV-TR diagnosis of SCZ
confirmed through medical records and the Mini International Neuropsychiatric Interview – Plus
edition (MINI-Plus) (1193). Patients were excluded from the study if they met diagnostic criteria
for a current mood disorder or substance use disorder within the past 3 months; had a history of
neurological or major medical disease; were experiencing significant akathisia (global rating of
>2 on the Barnes Akathisia Rating Scale) (1194) or extrapyramidal symptoms (3 or more ratings of >2 on the Simpson-Angus Rating Scale) (1195).

HC subjects had similar inclusion and exclusion criteria as the patients, but did not meet criteria for any current or previous Axis I disorders as per the MINI-Plus, or any Cluster A personality disorder as per the Structured Clinical Interview for DSM-IV Disorders – Axis II (SCID-II) (1232). Furthermore, control subjects reported no family history of a psychotic disorder.

All participants were right handed as determined using the Edinburgh Handedness Inventory (1233). The study protocol was approved by the institutional research ethics board and all participants provided written informed consent. All SCZ subjects were deemed competent to provide consent as per the MacArthur Competence Assessment Tool (1228).

6.2.2 Clinical Ratings

All participants were administered a battery of measures to assess psychopathology including: the Scale for the Assessment of Positive Symptoms (SAPS) (614); Scale for the Assessment of Negative Symptoms (SANS) (472); Calgary Depression Scale for Schizophrenia (CDSS) (649); Apathy Evaluation Scale – Clinician version (AES-C) (692); Quality of Life Scale - Abbreviated version (QLS-A) (868, 1197); Barrett Impulsiveness Scale (BIS-11) (1234); and the Snaith-Hamilton Pleasure Scale (SHAPS) (1235). Neurocognition was assessed using the MATRICS Consensus Cognitive Battery (MCCB) (1196).

6.2.3 Effort-based Decision Making Task

The task used in the present study was a modified version of the Effort Expenditure for Rewards Task (1006). Briefly, this is a multi-trial game that assesses participants’ willingness to expend effort for a monetary reward (Figure 6-1). On each trial, subjects choose to complete an “easy” button press trial or a “hard” trial. For the easy trials, subjects must press the L-key (on a standard keyboard) with their right (dominant) hand index finger a set number of times for 7 seconds to win $1.00. For the hard trials, subjects must press the S-key with their left (non-dominant) hand pinky finger a set number of times for 21 seconds to win $1.24-$4.30. Consistent
with the original paradigm (1006), the task used here ended after 20 minutes. Importantly, the maximum number of button presses for both the easy and hard trials was individually determined before the task. For this, subjects completed 4 trials with each hand where they were instructed to press the respective key as many times as possible. The trial with the lowest number of button presses was discarded, and the maximum button press rate was calculated as the mean from the remaining 3 trials. The button press criterion used in the actual task was individually set at 90% of the subject’s calculated maximum rate. This manipulation was done to control for non-specific differences in motoric ability between groups, and to assure that each individual had the capacity to complete the trials.

Figure 6-1. Diagram depicting the sequence of a single trial of the effort task

Trials begin with a fixation cue. Then, during the decision-phase, subjects are presented with information regarding the reward magnitudes of the easy and hard trial options and the probability of receiving a reward. Once subjects make a decision, they then proceed to the actual effort trial where they make button presses for an individually determined number of times in order to complete the task. Of note, subjects are able to track their progress through an illustrative bar which is progressively filled after each button press, with the top indicating
completion of the task. Participants are then shown feedback as to whether they completed the task and subsequently receive information of the monetary winnings for that trial.

In addition, subjects were not guaranteed the monetary reward following successful completion of a trial, rather the probability of winning varied at 12%, 50% and 88%. Participants were presented with these contingencies during the decision-making phase. As an incentive, subjects were told that they could win some bonus money at the end of the game depending on their performance. Before beginning the task, participants were asked to report their subjective valuation of income on a 5-point scale as well as how much they would value winning different amounts of money (0.1, 1, 10 and 100 dollars) using an 11-point scale. Responses to these latter questions were averaged to provide an overall valuation score. In addition, following the completion of the task, subjects were administered a post-experiment questionnaire designed to further assess participants’ valuations of the incentive (money) using a 10-point scale. The task was executed in MATLAB R2009b (Mathworks Inc., Natick, MA) running in Windows 7.

6.2.4 Reward Learning Task

Reward learning capacity was assessed using the learning phase of the probabilistic selection task (1050, 1236). Briefly, participants were presented with blocks of trials, in which three different stimulus pairs (AB, CD, EF) were presented in pseudorandom order. Consistent with a previous report (1050), the stimuli employed in the current study were images of common objects. Blocks consisted of 60 trials (20 per condition). Participants were instructed that certain stimuli had a higher chance of being correct, and their task was to select the stimuli that had the higher chance of being correct. Feedback followed choices to indicate whether the stimulus was correct or incorrect; however, this feedback was probabilistic. For example, in AB trials a choice of stimulus A lead to “correct” feedback in 80% of the trials, whereas a B selection lead to “incorrect” feedback in these trials (and vice versa for the remaining 20% of trials). CD and EF pairs were less reliable, with 70% and 60% correct feedback, respectively. Over the course of the learning phase, participants learned to select stimuli A, C and E more often and this indicated successful learning of reward contingencies. The learning phase was terminated when
participants achieved criterion for all three stimulus pairs in the same block, or after 6 blocks without sufficient learning. The discontinuation criteria, following previous reports (1050, 1236), were 65%, 60% and 50% correct in the AB, CD and EF conditions, respectively. This task was also run using scripts executed in MATLAB.

6.2.5 General Procedure

Participants completed study procedures across three study visits within a two-week timeframe. Clinical assessments were completed during the baseline visit by a single trained rater. Of note, the AES-C was administered by either the same (n=24) or an independent rater (n=8). Inter-rater agreement (i.e. scores within 1 point) was over 90%. During the next visit, participants underwent neuropsychological testing, and the effort and reward learning tasks were completed during the final visit. Participants received monetary compensation after each study session. Testing was done across multiple visits to limit potential mood-induction or fatigue confounds.

6.2.6 Statistical Analysis

Potential group differences on demographic variables were assessed using independent-sample t-tests or chi-square for continuous and categorical data, respectively. In instances where Levene’s test for equality of variances was rejected, degrees of freedom were adjusted accordingly. Effect sizes for between-group differences (Cohen’s d) were also computed (1237).

The primary analysis was designed to investigate whether group differences existed in willingness to expend effort across conditions and reward magnitude. This was tested using a 2 (group: SCZ and HC) x 2 (reward magnitude of hard option: high and low) x 3 (probability: 12%, 50% and 88%) repeated measures analysis of variance (ANOVA). Reward magnitude was dichotomized at the closest rounded integer value following both a mean and median split ($3). The dependant variable was the mean proportion of hard trials selected. In instances where Mauchly’s test of sphericity was rejected, Greenhouse-Geisser corrections were applied. Significant effects were further explored with a series of between-group one-way ANOVAs for each probability condition stratified by reward magnitude. Furthermore, to ensure the effects
revealed in the ANOVA models were not due to poor reward learning capacity, significant ANOVAs were repeated excluding individuals who failed to meet the reward learning criterion. Next, the measure of interest (proportion of hard trials selected) was submitted to correlational analyses within and across groups with other variables of interest, including chlorpromazine (CPZ) dosage equivalents (1199) for the SCZ group. Statistical significance was set at $\alpha < 0.05$ (two-tailed). Data were first processed using custom written scripts in MATLAB and then exported to PASW version 18 (SPSS Inc., Chicago, IL) for statistical analyses.

### 6.3 Results

#### 6.3.1 Sample Characteristics

Demographic and clinical information of the study sample are reported in Table 6-1. Groups did not differ in age, gender or ethnicity. Of note, the SCZ group was significantly more apathetic (AES-C; $t_{18.4} = 5.81$, $p < 0.001$, $d = 2.07$) and had lower psychosocial functioning (QLS-A; $t_{19.8} = 8.76$, $p < 0.001$, $d = 3.15$). Also, importantly, the groups did not differ on hedonic capacity (SHAPS: $t_{30} = 0.66$, $p = 0.51$, $d = 0.24$).

<table>
<thead>
<tr>
<th>Table 6-1. Demographic and clinical characteristics of study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy controls (n=16)</strong></td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
</tr>
<tr>
<td>Ethnicity, Number</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>African-Canadian</td>
</tr>
<tr>
<td>South-Asian</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Data is presented as means and standard deviations, unless otherwise specified.

*Group difference significant at p<0.05, or **p<0.01

Abbreviations: SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; CDSS: Calgary Depression Scale for Schizophrenia; AES-C: Apathy Evaluation Scale – Clinician version; MCCB: MATRICS Consensus Cognitive Battery; QLS-A: Quality of Life Scale – Abbreviated version; BIS-11: Barratt Impulsiveness Scale; SHAPS: Snaith-Hamilton Pleasure Scale; CPZ Equivalents: Chlorpromazine equivalents estimated following Andreasen et al. (2010).
Note: All patients received atypical antipsychotic monotherapy, except for one individual who received an atypical plus typical combination. Other concomitant medication included: antidepressant (n=4), anticholinergic (n=3), benzodiazepine (n=4), and mood stabilizer (n=2).

6.3.2 Main Results of Effort Task

Patients had significantly lower maximum button press rates on easy (SCZ: mean = 28.9, SD = 4.8; HC: mean = 36.3, SD = 3.8; t30 = 4.83, p < 0.001, d = 1.71) and hard trials (SCZ: mean = 86.0, SD = 14.5; HC: mean = 108.0, SD = 11.0; t30 = 4.85, p < 0.001, d = 1.71). The number of trials completed during the task did not differ between SCZ and HC (SCZ: mean = 53.4, SD = 7.6; HC: mean = 52.1, SD = 4.9; t30 = 0.11, p = 0.91, d = 0.04); moreover, the percentage of trials successfully completed during the main task did not significantly differ between groups (SCZ: mean = 0.94, SD = 0.10; HC: mean = 0.99, SD = 0.03; t16.8 = 1.69, p = 0.11, d = 0.61).

The three-way repeated-measures ANOVA revealed a significant main effect of probability (F1.3, 39.3 = 38.42, p < 0.001), a main effect of reward magnitude (F1, 30 = 38.68, p < 0.001), but no main effect of group (F1, 30 = 2.49, p = 0.13). Also, there was a significant interaction between group and reward (F1, 30 = 14.56, p = 0.001), group and probability (F1.3, 39.3 = 9.03, p = 0.002), but no three-way interaction (F2,60 = 0.98, p = 0.38). Curiously, there was also no interaction between reward and probability (F2,60 = 0.53, p = 0.59). These data are graphically depicted in Figure 6-2.
Figure 6-2. Graphical depiction of mean proportion of hard trials selected stratified by group across conditions and reward magnitude: (a) low rewards and (b) high rewards

Error bars depict standard errors. Schizophrenia (SCZ) subjects are coded in dark shading and healthy controls (HC) in light shading.

For low-reward trials, post-hoc one-way ANOVAs revealed no significant group difference on 50% (F1,30 = 1.53, p = 0.23, d = 0.18), or 88% trials (F1,30 = 0.25, p = 0.62, d = 0.44). However, there was a significant difference for 12% trials (F1,30 = 6.67, p = 0.02, d = 0.92), suggesting SCZ subjects selected hard trials more often than HC during these trials of lowest incentive value.

During high-reward trials, post-hoc one-way ANOVAs revealed no significant group difference during 12% trials (F1,30 = 0.28, p = 0.60, d = 0.19). However, groups significantly differed in their willingness to expend effort during 50% (F1,30 = 18.54, p < 0.001, d = 1.52) and 88% trials (F1,30 = 10.36, p = 0.003, d = 1.14), suggesting individuals with SCZ were less willing to expend effort for these high incentive trials.

To confirm our manipulation of incentive value was effective, a separate repeated-measure ANOVA model was computed for each group and linear contrasts were examined. Both groups...
demonstrated significant linear relationships with probability (SCZ: $F_{1, 15} = 8.06$, $p = 0.01$; HC: $F_{1, 15} = 46.37$, $p < 0.001$).

To rule out potential fatigue effects, analyses were repeated including only the first 30 trials completed, and the findings were unchanged (data not shown).

6.3.3 Pre- and Post-Experiment Questionnaire

Patients and controls did not differ in their perception of their monetary income ($t_{30} = 0.81$, $p = 0.43$, $d = 0.30$) or in their subjective valuation of the monetary reward (SCZ: mean = 5.8, SD = 1.7; HC: mean = 4.8, SD = 1.6; $t_{30} = 1.58$, $p = 0.12$, $d = 0.58$). Moreover, consistent with the pre-experiment findings, SCZ and HC did not differ in their post-experiment valuation of the monetary incentive ($t_{30} = 0.09$, $p = 0.93$, $d = 0.03$).

6.3.4 Effect of Reward Learning Capacity

Three SCZ and one control participant failed to meet the reward learning criterion. The significant group differences of willingness to expend effort remained so, even when these individuals were excluded from the analysis for both 50% ($F_{1, 26} = 12.47$, $p = 0.002$), and 88% high-reward trials ($F_{1, 26} = 5.40$, $p = 0.03$). The group difference during low-reward 12% trials also remained ($F_{1, 26} = 4.33$, $p = 0.05$).

6.3.5 Correlational Analyses

Within the SCZ group, there were no significant correlations between proportion of hard trials selected during the high-reward 50% or 88% conditions and any clinical variable, including CPZ equivalents (all $p>0.05$). For the low-reward 12% trials, BIS-11 scores were the only variable significantly correlated with proportion of hard trials selected ($r = 0.52$, $p = 0.04$). Repeating these correlations collapsing across groups did reveal several significant relationships (Table 6-2). Of note, the proportion of hard trials selected during high-reward 50% and 88% trials both
correlated with apathy (50%: r = -0.47, p = 0.01; 88%: -0.45, p = 0.01) and neurocognition (50%: r = 0.48, p = 0.005; 88%: 0.54, p = 0.001).

Table 6-2. Bivariate correlations across groups

<table>
<thead>
<tr>
<th></th>
<th>LR 12%</th>
<th>HR 50%</th>
<th>HR 88%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES-C</td>
<td>0.49**</td>
<td>-0.47**</td>
<td>-0.45**</td>
</tr>
<tr>
<td>SAPS</td>
<td>0.12</td>
<td>0.21</td>
<td>0.10</td>
</tr>
<tr>
<td>CDSS</td>
<td>0.48*</td>
<td>-0.28</td>
<td>-0.42*</td>
</tr>
<tr>
<td>BIS-11</td>
<td>0.52**</td>
<td>-0.30</td>
<td>-0.37*</td>
</tr>
<tr>
<td>SHAPS</td>
<td>-0.16</td>
<td>0.41*</td>
<td>0.35</td>
</tr>
<tr>
<td>MCCB</td>
<td>-0.42*</td>
<td>0.49**</td>
<td>0.54**</td>
</tr>
<tr>
<td>QLS-A</td>
<td>-0.36</td>
<td>0.48**</td>
<td>0.40*</td>
</tr>
<tr>
<td>Handedness</td>
<td>-0.07</td>
<td>0.18</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Correlations are significant at p<0.05, or **p<0.01

Abbreviations: LR: Low-reward trials; HR: High-reward trials

6.4 Discussion

In the current study, we employed a novel translational paradigm to behaviourally demonstrate motivational deficits among individuals with SCZ. In this effort a number of findings emerged. First, patients were found to be much less willing to expend effort compared to HC, especially when the incentive was high. These deficits are related to both amotivation and neurocognitive
impairments. Second, for the lowest incentive trials patients seemed to be more willing to expend effort, which was related to the impulsiveness of the patient sample. Next, our findings of incentive motivation deficits were not simply secondary to impaired reward-based stimulus-outcome learning, and were observed despite intact hedonic capacity. Taken together, our findings demonstrate incentive motivation behavioural deficits that are likely subserved by impairments in cost-benefit (specifically effort cost) computations.

It is worth underscoring that our patient sample did not differ in their subjective valuations for the monetary reward, which is consistent with previous findings of patients with SCZ reporting intact in-the-moment experience and consummatory pleasure (1088, 1098, 1099, 1238); thus, our findings are consistent with the notion of patients having deficits in mobilizing volitional systems in pursuit of a reward (902). Stated another way, patients expressed valuing the reward to a similar degree as controls, yet they failed to respond optimally. Importantly, we are unable to attribute this apathy to impairments in patients' ability to select the higher value option, as the deficits persisted even when we restricted the analyses to patients with intact reward learning capacity. Moreover, it may be inaccurate to suggest that patients simply did not care about responding to the task (i.e. responded randomly), as patients showed a linear increase in the probability of selecting the more effortful option as the incentive increased.

Previous research has proposed that motivational deficits in SCZ may represent a impairment in the representation of value (1071). To this end, a recent study reported deficits in effort-based decision making among individuals with SCZ relative to HCs and concluded that the observed deficits may be due to both alterations in effort computation and value representations (904); however, this study did not assess for any reward-related constructs other than effort-based decision making. The present study extends these previous findings by demonstrating similar behavioural effort-based impairments in the face of intact reward valuation (and hedonic capacity). Our findings are thus consistent with the suggestion that motivational deficits in SCZ are related to abnormalities in effort computations rather than reward valuation. It is noteworthy that both the present study and that of Gold et al. (2013) report findings of deficits in patients' willingness to expend effort for high-probability large rewards. It is also interesting to note that our behavioural findings mimic those of a recent study using a pre-clinical model of negative symptoms that demonstrated intact valuation yet impaired willingness to expend effort (978).
Impairments in willingness to expend effort were related to both apathy and neurocognitive deficits. This latter finding is interesting and consistent with previous literature demonstrating a relationship between apathetic behaviour and cognition in patients with SCZ (712, 850). Moreover, the study by Gold et al. (2013) also found neurocognition to be related to willingness to expend effort. Previous work has shown that effort may influence cognitive performance (1131), however, these two constructs have also been shown to be conceptually independent (663). Future work should disentangle the influence of both apathy/amotivation and neurocognition on effort-based decision making.

As an additional control in our study, we individually calibrated the number of motor responses that denoted successful completion of a trial. This ensured that any non-specific differences in motor speed (e.g. psychomotor slowing) were minimized. Given this, as well as our exclusion of patients experiencing motor-related medication side effects, suggests that our finding of incentive motivation deficits are not simply an artifact of impaired motor ability. This control is of critical importance as most of our inferences on incentive motivational systems depend on instrumental responses (908). Hence any individual differences in motor ability will bias the caliber to which the instrumental response is executed, which may in turn be incorrectly interpreted as decreases in motivated behaviour.

It is of note that the largest group difference in incentive motivation deficits emerged in trials with the greatest uncertainty (i.e. 50% probability trials). This is particularly intriguing given previous studies demonstrating that neural responses, especially dopaminergic activity, covary with reward probability (1239, 1240). A dopaminergic underpinning of the observed motivational deficit is consistent with our hypothesis, although at face value this seems to call into question the validity of the current findings given the patient sample was receiving dopamine antagonists. A few points, though, argue against the notion that our findings are secondary to antipsychotic exposure. First, all patients were receiving atypical antipsychotics, and with the exception of one, were on monotherapy, thereby minimizing effects on reward-related neural responses (1162). Second, we failed to find a significant linear relationship between antipsychotic dose and decisions to expend effort. Lastly, patients did not demonstrate a general reduction in their willingness to expend effort (i.e. for every incentive value); rather, the deficits emerged selectively for high incentive trials. This selectivity suggests that the results are
due to impairments in specific computations during cost-benefit decision-making, rather than a pervasive devaluation of reward value by effort cost regardless of the decision at hand.

Deficits in willingness to expend effort for reward are certainly a clinical concern. Many patients with SCZ, including those included in the present study, evidence poor psychosocial functioning, which has been associated with negative symptoms such as apathy (850, 875, 876). Although patients are offered rehabilitation programs, they are often not motivated to engage in such programs (1241). The present results echo this clinical reality as we demonstrate that offering patients’ money in exchange for effort, a paradigm analogous to some temporary labour jobs, was quite unsuccessful. Indeed, this was observed when the incentive was high (i.e. large-reward and 88% probability trials). Initial screening of individuals entering such programs may benefit from employing an objective effort task such the one used in the present study.

In evaluating the present study, some limitations should be addressed. Firstly, the sample size was modest. Nevertheless, the observed effect sizes were quite large (e.g. $d = 1.5$ for the 50% high-incentive trials) and we were sufficiently powered to detect such large effects (i.e. $d>1.0$); larger studies are still needed to rule the possibility of false negatives. Second, all patients were taking antipsychotic medications rendering any inference about the drug-free state impossible. That said, the clinical reality remains that most individuals with SCZ are on such medications; hence, our results can be interpreted as demonstrating incentive motivation deficits in "real-world" patients. Also, the version of the effort task employed in the present study conflates effort and time in that trials of greater effort also require more time to complete. Although the present data do not allow us to conclusively rule out the possibility that our findings are influenced by temporal delay rather than effort, a couple of points do argue against this contention: 1) choice of hard trials did delay feedback of reward receipt, but receipt of the actual reward occurred at the end of the session, thereby minimizing effects of delay costs; 2) subjects made relatively quick decisions of whether to complete hard trials, which precludes careful deliberation and calculation of an optimal strategy based on all variables (i.e. reward value, probability, effort cost, delay) (1006). Indeed, pre-clinical studies have dissociated these two processes (962); future studies assessing effort should attempt to control for other response costs as well the potential for "strategic" decision making. Lastly, in our assessment of incentive motivation we employed a single behavioural measure using money as a reward. The ubiquity of the observed motivational deficits across different rewards (e.g. food, sex, etc.) remains to be seen.
Our findings here affirm motivational impairment in SCZ using an objective translational paradigm. Employing such a paradigm, coupled with functional neuroimaging, may be well suited to delineate the underlying neurobiology of this observed deficit in the willingness to expend effort. The relative contributions of the mesolimbic dopaminergic system and the cortical anterior cingulate gyrus, among other regions including the orbitofrontal cortex, in subserving this deficit remain unknown. It may well be that connectivity between these regions is crucial for calculating effort cost; indeed, previous work has shown covariance within this network among patients with SCZ (1242), and there is some evidence from rodents that these effort-based decision-making deficits may be related to cortical-striatal connectivity (997). Nonetheless, the neurobiological mechanisms of the incentive motivation deficits, specifically related to cost-benefit decision-making and effort, demonstrated here remain to be elucidated.
Chapter 7

7 Deconstructing Goal-directed Behaviour: A Concurrent Evaluation of Hedonic Experience, Reward Learning, and Effort Cost Computations in Early Schizophrenia

7.1 Introduction

Impairments in the drive toward, initiation and persistence in goal-directed activities (i.e., amotivation) are a prevalent feature of schizophrenia, even in the early stages of illness (1200, 1225). Early descriptions of schizophrenia figured a prominent role for these and related (i.e., negative) symptoms in the fundamental nature of the illness (14, 23). Recent work has reaffirmed the importance of these symptoms, especially motivational deficits, by highlighting their prognostic value in determining functional outcomes (607, 839, 845, 850, 865, 866, 873, 874, 876, 891, 1200). Despite the known burden and disability associated with these symptoms, a fundamental understanding of the underlying mechanisms, as well as effective treatment options, remains elusive.

Several proposals have been advanced to account for the expression and persistence of motivational deficits, each with varying degrees of empirical support. Many of these proposals have revolved around specific reward processing impairments, perhaps due to their intuitive appeal and conceptual relationship to clinical apathy, at least at face value. Examples include impairments in valuation of outcomes, deficits in ability to learn the value of outcomes and the link between actions and outcomes and, more recently, overestimation of the costs related to obtaining a valued outcome (881-884, 889). Theoretically, abnormalities in any one of these computational processes could undermine goal-directed action, which would in turn manifest as clinical apathy (i.e., motivational deficits). For the most part, studies to date have been designed to examine whether any one of these might individually represent a candidate computational process underlying the motivational deficits of schizophrenia, without taking into account concurrent or alternative processes. There are some notable exceptions; for example, one study
evaluating effort discounting in patients with schizophrenia concurrently evaluated hedonic experience using objective tasks to examine inter-relationships between these processes (1243). In another study, carried out by our group, we examined effort-based decisions, reward learning, and subjective accounts of reward valuation concurrently, and found evidence for effort-based impairments that existed independent of these other reward processes (1221). We argue such comprehensive assessments are important in advancing our understanding of underlying processes of motivational deficits.

In the present study we sought to further examine the relationship between multiple reward processes and motivational deficits in patients with schizophrenia. Specifically, we examined multiple key reward processing variables, whose selection was guided by recommendations put forth as a part of the Research Domain Criteria (RDoC) initiative (1103, 1105). Specifically, we used the positive valence systems matrix to select objective assessments relevant to motivational deficits. Domains evaluated included reward valuation, effort valuation (i.e., effort cost computations), reward learning, and action selection (i.e., preference- or value-based decision making). In carrying out this work, we had several hypotheses. First, we hypothesized that patients would demonstrate impairments in several of the evaluated reward processes but, importantly, would not differ on all; for example, we did not anticipate group differences in reward valuation or in-the-moment hedonic experience (1099, 1238). Second, based on our previous study (1221), we hypothesized that patients would demonstrate impairments in effort cost computations that would be present even in the face of other reward deficits. Finally, we hypothesized that at least one, and perhaps several, of these reward variables would be related to clinically-rated motivational deficits in patients.

7.2 Methods and Materials

7.2.1 Participants

Fifty-eight outpatients with schizophrenia and 58 individually age- (±3 years) and sex-matched healthy controls participated in the present study. Patients were recruited from outpatient clinics at the Centre for Addiction and Mental Health in Toronto, Ontario, Canada and met DSM-IV-TR criteria for schizophrenia (N=53) or schizoaffective disorder (depressed subtype, no current
mood episode; N=5) confirmed using the Mini International Neuropsychiatric Interview (MINI) (1193) and through medical records. Inclusion criteria for all participants included age at the time of testing between 18 and 35 years, fluency in English, right-handedness confirmed using the Edinburgh Handedness Inventory (1233), absence of any serious and unstable physical medical illness as well as any neurological condition (e.g., traumatic brain injury with neuropsychological sequelae). All patients were clinically stable, with no inpatient hospitalizations within the past 3 months, and did not have any changes to their psychotropic medication regimen for at least the preceding 4 weeks. To minimize potential confounds in the assessment of negative symptoms and decision making in patients, several other criteria were added. We included only patients who demonstrated reasonable overall decision making capacity and did not demonstrate gross impairments in reasoning and judgement as determined by the MacArthur Competence Assessment Tool (MacCAT) (1228); received atypical antipsychotic monotherapy; were not experiencing prominent medication-related extrapyramidal side effects (i.e., global score of greater than 2 on the Barnes Akathisia Rating Scale (1194) or more than 2 ratings of greater than 2 on the Simpson-Angus Scale (1195)); and, did not meet criteria for an Axis I disorder apart from schizophrenia or schizoaffective disorder (e.g., major depressive disorder, obsessive-compulsive disorder, substance dependence within the past 3 months). Finally, we included only patients early in course of the illness (i.e., age less than 35 years and emphasis on patients with a duration of illness between 1 and 5 years) to avoid chronic illness effects (e.g., extended institutionalization, prolonged unemployment).

The inclusion and exclusion criteria for healthy control subjects was similar but, in addition, healthy control participants: did not meet criteria for any Axis I disorder, confirmed using the MINI; were not receiving any psychotropic medications; did not endorse a high level of schizophrenia-like traits, confirmed using the Schizotypal Personality Questionnaire (SPQ) (1244); and did not report a positive family history of a psychotic disorder.

The study protocol was approved by the institutional Research Ethics Board, and all participants provided written informed consent. Notably, all patients were deemed competent to provide consent as per the MacCAT (1228).
7.2.2 Clinical Ratings

Severity of psychopathology for patients with schizophrenia was evaluated using the anchored version of the Brief Psychiatric Rating Scale (BPRS) (1230), the Scale for the Assessment of Negative Symptoms (SANS) (524), and the Calgary Depression Scale for Schizophrenia (CDSS) (650). Functional status was evaluated using the 4-item abbreviated version of the Quality of Life Scale (QLS-A) (869).

In addition, all participants were administered a battery of assessments. Motivational deficits were evaluated using the clinician version of the Apathy Evaluation Scale (AES-C) (692). Global neurocognition was evaluated using the Brief Neurocognitive Assessment (BNA) for schizophrenia (1245, 1246). Hedonic capacity was evaluated using the Snaith-Hamilton Pleasure Scale (SHAPS) (1235). Finally, defeatist performance beliefs were evaluated using the dysfunctional attitudes scale (DAS) (815, 1247).

7.2.3 Effort-based Decision Making Task

The effort-based decision making task used in the present study represents a previously validated measure (1248). This task is a multi-trial "game" that evaluates participants' willingness to expend effort in exchange for monetary reward (i.e., incentive motivation). On each trial, participants have the opportunity to select either an "easy" or "hard" trial. For an easy trial, subjects must press the L-key (on a standard computer) with the index finger of their dominant (i.e., right) hand a fixed number of times. For hard trials, subjects must press the S-key a set number of times with the pinky finger of their non-dominant (i.e., left) hand. Each of these trials lasts 10 seconds and subjects cannot pre-maturely advance, which effectively equates the total trial duration (i.e., temporal delay costs between these 2 trial types). The easy trial was always worth $1.00, whereas there were 10 possible values for the hard trial option ranging from $1.50 to $6.00 in $0.50 increments. Probability of receiving reward was also varied at 3 levels (10%, 50%, 90%), and each reward magnitude for the hard trial option was presented once for each probability level, resulting in a total number of 30 trials. The requisite number of button presses (i.e., effort) was individually calibrated for each participant; before beginning the task, participants' maximum button pressing rate for their nondominant hand was evaluated across 3
trials where they were instructed to press the respective key as many times as possible (1221, 1248). The highest value across the 3 trials was used as the maximum rate, and the button press criterion for easy and hard trials was based on this personalized value. Specifically, the hard task required 80% of the subject's calculated maximum rate, whereas the easy task required half this number. This manipulation was done to control for non-specific differences in motoric ability between groups, and to assure that each individual had the capacity to complete the trials. To serve as an incentive, participants were told that they would receive a monetary payout (i.e., a bonus payment) at the end of the visit that was contingent on their task performance. The task was executed in MATLAB R2009b (Mathworks Inc., Natick, MA) using PsychToolbox (1249) running in Windows.

Before beginning the task, participants were asked to report their subjective valuation of their personal income as well as how much they would value winning different amounts of money (0.1, 1, 10 and 100 dollars) using an 11-point scale. Responses to these latter questions were averaged to provide an overall reward valuation score (1221). In addition, following the completion of the task, subjects were administered a post-experiment questionnaire designed to further assess participants’ valuations of the incentive (i.e. money) also using an 11-point scale.

Furthermore, and also before the actual task, participants completed 4 practice trials to ensure familiarity and comprehension of the task. Participants were also instructed to complete both the easy and hard trials during these practice sessions to ensure they realized the effort required of each trial type. Directly following the main effort-based decision making task, that is after the main 30 trials, participants completed another separate effort-based reward-driven choice task (i.e., a simple value-based decision making task). This task only involved 4 trials to eschew potentially compounding fatigue across tasks. Also, this task only manipulated the reward value and kept the effort demands constant; that is, there were only 2 hard options, one of which had a higher potential reward than the other. Rationally, all participants should always select the higher reward option, with selection of the lower reward option suggesting gross deficits in simple value-based decision making, motoric limitations, suboptimal understanding of task instructions, or some other confound that obstructs inferences about cost-benefit decision making during the main task. This post-experiment task was adopted from an analogous pre-clinical paradigm (959, 987, 989).
After these tasks, participants completed another calibration run with their non-dominant pinky finger to evaluate potential fatigue effects. For this, participants were asked to use their nondominant pinky finger to press the button as fast as they could. If participants were able to press the number of presses required during the task directly following the task, we inferred that their decisions were not based on (muscular) fatigue, but rather reflected their integration of costs and benefits associated with each choice.

### 7.2.4 Reward Learning Task

Reward learning was assessed using a probabilistic stimulus selection task (1236). The version of the task used in the present study employed images of common objects to aid encoding, consistent with previous reports (1050, 1250). Briefly, participants were presented with three different stimulus pairs (AB, CD, and EF), which were presented in pseudorandom order. The learning phase of the task was comprised of 60 trials (20 per condition). Participants were instructed that certain stimuli had a higher chance of being correct, and that their task was to select the stimulus in each pair that they felt had the highest chance of being correct. Following participants' choices, feedback was provided to indicate whether the selected stimulus was correct or incorrect; however, the provided feedback was probabilistic. For AB trials a choice of stimulus A lead to “correct” feedback in 80% of the trials, whereas selection of stimulus B led to “incorrect” feedback in these trials (and vice versa for the remaining 20% of trials). CD and EF pairs were less reliable, with 70% and 60% correct feedback, respectively. Over the course of the learning phase, participants learned to select stimuli A, C and E more often and this indicated successful learning of reward contingencies.

Overall learning performance was quantified using the proportion of stimuli selected across all pairs that were considered more valuable (i.e., A, C, and E choices). Participants were also categorized as having intact learning capacity if they learned to select the most valuable stimulus (A) over the least valuable stimulus (B), operationalized as selection of A over B for greater than 50% of trials. Beyond overall learning of acquisition of stimulus-outcome contingencies, we also examined metrics reflective of participants' ability to rapidly and rationally utilize feedback information to guide their subsequent choices. Specifically, we computed rates for "win-stay" (i.e., decisions to select a stimulus following correct feedback during the previous exposure), and
"lose-shift" choice behaviour (i.e., decision to select the alternative stimulus following incorrect feedback during the previous exposure). This task was executed in MATLAB, using the PsychToolbox (1249).

7.2.5 Reward Valuation Task

To assess hedonic responsivity, participants provided in-the-moment pleasantness ratings in response to a selection of pictures, drawn from the International Affective Picture System (IAPS) (1251). Thirty-six images were drawn from the IAPS database based on normative emotional experience ratings. Specifically, 12 positive (IAPS stimulus numbers: 1610, 2370, 4598, 5000, 5010, 5200, 5831, 8030, 8185, 8370, 8490, 8502), 12 neutral (IAPS stimulus numbers: 1670, 2382, 2410, 2880, 2980, 5534, 5661, 7004, 7010, 7175, 7490, 7560), and 12 negatively valenced images (IAPS stimulus numbers: 1300, 5971, 6010, 6260, 6300, 9001, 9220, 9230, 9331, 9404, 9561, 9622) were selected and, notably, none of the images contained potentially offensive content such as erotic content or images of mutilation. Images were presented for 6 seconds, and after this an image of the IAPS Self-Assessment Manikin appeared (1252, 1253), indicating that a response could now be registered. Participants' were instructed to rate each image based on how the stimulus made them feel (i.e., their subjective reaction). Ratings were made on a Likert-type scale with scores ranging from 1 (i.e., extremely unpleasant) to 9 (i.e., extremely pleasant); scores of 5 represented neutrality. Stimuli were presented in a pseudorandom order with images spanning the valence categories inter-mixed. This task was also executed in MATLAB, using the PsychToolbox (1249).

7.2.6 General Procedure

Participants completed the study procedures during a single study visit. The diagnostic and clinical assessments were administered first, after which the subjects completed the objective reward processing tasks. Between the clinical and behavioural sessions, participants were instructed to take a break to minimize fatigue and any potential adverse reactions to the clinical interview (e.g., mood-induction effects). Participants received monetary compensation at the end of the visit for their participation in the study.
7.2.7 Statistical Analyses

Potential group differences on sociodemographic or clinical variables were assessed using independent-samples t-tests or chi-squared tests for continuous and categorical data, respectively. Next, we quantified the prevalence of clinically significant motivational deficits in our patient sample; prominent motivational deficits were defined using a cut off score on the AES-C that was 2 standard deviations above the mean score of the control group (874, 1254). Patients with a score of 35 or greater were considered to have a clinically significant level of apathy.

We first examined performance on each test separately. For the effort-based decision making task, we first examined whether the task was effective in having participants expend effort in exchange for reward. This was done by evaluating whether participants in each group were more likely to select the hard trial option for the higher value trials (indexed by the 90% condition) versus the lower value condition (indexed by the 10% condition), which would suggest appropriate incentive effects (1248). We next explored the effect of reward (i.e., probability and monetary amount) on effort performance using a 3-by-2 -by-2 repeated measures analysis of variance (ANOVA) model, which included group status as a between-subjects factor. Reward values were binned into small and large values following a median split (1248). Simple-value based decision making was quantified using the number of hard trials selected during this task and because of the restricted number of trials, we were primarily interested in a binary classification (optimal versus suboptimal responses). Optimal responders were defined as those participants who selected the high-value option over the low-value option for each trial, and the remaining participants were classified as suboptimal responders for this task. Group differences in the reward learning variables were examined using independent-samples t-tests. The percentage of participants that learned to select stimulus A over B were noted, and rates of participants with intact reward learning capacity were compared across groups using a chi-squared test. Hedonic experience (i.e., reward valuation) was examined using a 3-by-2 repeated-measures ANOVA model, with stimulus valence as a within-subjects factor and group as a between-subjects factor. Consistent with previous work (1221), we examined whether potential group differences in effort performance would hold in subgroups of participants with adequate
performance on selected other tasks. We also examined the inter-relationships between the reward variables using Spearman's rank correlations.

Beyond the subgrouping approach, we were also interested in which of the reward variables contributed to patient-control group differences. To this end, we computed a logistic regression model with group membership as the dependent variable, and the reward variables as predictor variables. This model provides insights into the independent predictive value of each reward processing variable for group classification/discrimination.

Following the analyses on group differences, we turned to the examination of reward-related correlates of clinical amotivation ratings in patients with schizophrenia. For this, we first examined potential bivariate relationships between reward variables and clinically-rated motivational deficits using Spearman's rank correlations. The relationship with other clinical variables was also explored using this approach. Neurocognition scores were transformed to age- and sex-matched Z-scores based on normative data (1246). Expressive negative symptoms were evaluated using the sum of the affective flattening subscale (excluding the global item) and the poverty of speech item from the SANS. Positive symptom and disorganization severity were also evaluated using the thought disturbance and disorganization factors, respectively, derived from the BPRS (1229). Finally, antipsychotic dosage equivalents were computed using chlorpromazine equivalents (1231).

Statistical tests were considered significant at a p-value of less than 0.05 (two-tailed). Data were initially processed using custom written scripts in MATLAB, and subsequently analyzed using SPSS Statistics version 20 (IMB Corp., Armonk, NY, USA).

7.3 Results

7.3.1 Participant Characteristics

Sociodemographic and clinical characteristics of the sample are presented in Table 7-1. The groups were individually age- and sex- matched, and in addition there were no group differences in degree of right-handedness, parental education (a proxy indicator of socioeconomic status), although patients did have significantly less personal education relative to healthy controls
Patients on average endorsed a lower level hedonic capacity and more defeatist performance beliefs. Healthy control subjects were less apathetic and performed better on cognitive tests.

Table 7-1. Sociodemographic and clinical characteristics of the study sample (N = 58 per group)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (N=58)</th>
<th>Healthy controls (N=58)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Mean (S.D.) or %</td>
<td>Mean (S.D.) or %</td>
</tr>
<tr>
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<td>25.9 (3.3)</td>
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<td>70.7</td>
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<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
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<tr>
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<td>Schizoaffective disorder</td>
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<td>-</td>
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<tr>
<td>Duration of Illness (years)</td>
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<td>-</td>
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<td>Participant's Education (years)</td>
<td>13.6 (2.0)</td>
<td>15.9 (2.0)***</td>
</tr>
<tr>
<td>Father's Education (years)</td>
<td>14.5 (2.8)</td>
<td>14.9 (3.2)</td>
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<tr>
<td>Mother's Education (years)</td>
<td>14.2 (2.6)</td>
<td>14.1 (2.4)</td>
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<tr>
<td>Highest Parental Education (years)</td>
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<td>15.3 (2.7)</td>
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<tr>
<td>Handedness</td>
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</tr>
<tr>
<td>Antipsychotic dosage (chlorpromazine) equivalents</td>
<td>496.2 (190.4)</td>
<td>-</td>
</tr>
<tr>
<td>Measure</td>
<td>Value 1</td>
<td>Value 2</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>SAS EPS Total</td>
<td>2.8 (3.2)</td>
<td>-</td>
</tr>
<tr>
<td>Akathisia Global</td>
<td>0.3 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>BPRS Total Score</td>
<td>31.4 (6.6)</td>
<td>-</td>
</tr>
<tr>
<td>BPRS Positive symptoms</td>
<td>7.3 (3.4)</td>
<td>-</td>
</tr>
<tr>
<td>BPRS Disorganization symptoms</td>
<td>5.4 (2.2)</td>
<td>-</td>
</tr>
<tr>
<td>SANS Total Score</td>
<td>33.2 (19.8)</td>
<td>-</td>
</tr>
<tr>
<td>SANS Diminished Expression Score</td>
<td>9.9 (7.7)</td>
<td>-</td>
</tr>
<tr>
<td>CDSS Total</td>
<td>1.0 (1.4)</td>
<td>-</td>
</tr>
<tr>
<td>QLS-A</td>
<td>3.2 (1.3)</td>
<td>-</td>
</tr>
<tr>
<td>AES Total</td>
<td>38.8 (10.2)</td>
<td>26.1 (4.4)</td>
</tr>
<tr>
<td>BNA Standardized Z-score</td>
<td>-1.0 (0.9)</td>
<td>0.4 (0.9)</td>
</tr>
<tr>
<td>SHAPS</td>
<td>47.2 (5.0)</td>
<td>50.3 (4.3)</td>
</tr>
<tr>
<td>DAS</td>
<td>47.0 (14.6)</td>
<td>34.5 (11.7)</td>
</tr>
</tbody>
</table>


**Note:** All patients were receiving atypical antipsychotic monotherapy (Aripiprazole, N=9, Clozapine, N=16, Olanzapine, N=6, Paliperidone, N=14, Quetiapine, N=1, Risperidone, N=12).
Other concomitant medications included: antidepressants (N=12), anticholinergics (N=7), benzodiazepines (N=5), and mood stabilizers (N=3).

Group differences are statistically significant at *P < 0.05, **P < 0.01, or *** P < 0.001

Forty of the 58 (69%) patients evidenced prominent motivational deficits. These individuals also had significantly more severe scores on the avolition/apathy global item of the SANS (t = 5.36, p < 0.001) but, notably, were not more ill across all domains of psychopathology; patients with prominent motivational deficits did not evidence more severe positive symptoms or disorganization (both p's > 0.10).

7.3.2 Effort-based Decision Making

Patients had significantly slower maximum button press rates, and were thus required to make less button taps during the actual task relative to the healthy controls (Table 7-2). Notably, though, patients' maximum button pressing rate was not related to their decisions to expend effort (r = 0.14, p = 0.32). No participant invariably selected the easy option; however, 8 (13.8%) controls and 2 (3.4%) patients did select the hard option for each trial during the task. The groups did not differ in their subjective valuation of reward when asked before initiating the task, but when asked about the value of reward presented during the task specifically, patients reported valuing these more than healthy controls (Table 7-2). In assigning subjective value scores to the prospect of winning different amounts of money, all subjects reported valuing the largest monetary amount more than the lowest monetary amount (with the exception of one control participant who reported equally high values for each amount). This result suggests that all participants did indeed value the rewards, and were able to make very simple choices based on subjective value; in other words, all subjects made appropriate simple preference-based choices.

<p>| Table 7-2. Performance metrics for the effort-based decision making task |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia (N=58) Mean (S.D.)</th>
<th>Healthy controls (N=58) Mean (S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Button Press Rate</td>
<td>58.7 (9.5)</td>
<td>67.1 (7.7)***</td>
</tr>
<tr>
<td>Task requirements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required Presses for Easy Task</td>
<td>23.9 (3.8)</td>
<td>27.2 (3.1)***</td>
</tr>
<tr>
<td>Required Presses for Easy Task</td>
<td>47.4 (7.6)</td>
<td>54.1 (6.1)***</td>
</tr>
<tr>
<td>Task Performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of Hard Trials Selected (Total)</td>
<td>0.56 (0.19)</td>
<td>0.71 (0.17)***</td>
</tr>
<tr>
<td>Proportion of Hard Trials Selected (10%)</td>
<td>0.30 (0.24)</td>
<td>0.45 (0.30)**</td>
</tr>
<tr>
<td>Proportion of Hard Trials Selected (50%)</td>
<td>0.62 (0.25)</td>
<td>0.76 (0.20)**</td>
</tr>
<tr>
<td>Proportion of Hard Trials Selected (90%)</td>
<td>0.76 (0.22)</td>
<td>0.92 (0.13)***</td>
</tr>
<tr>
<td>Pre-task questionnaires</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective valuation of income</td>
<td>5.2 (2.5)</td>
<td>4.6 (2.3)</td>
</tr>
<tr>
<td>Subjective valuation of money</td>
<td>4.9 (1.5)</td>
<td>5.0 (1.7)</td>
</tr>
</tbody>
</table>
Post-task questionnaires

Subjective valuation of reward

7.6 (1.7) 6.5 (2.5)*

Group differences are statistically significant at *P < 0.05, **P < 0.01, or *** P < 0.001

The incentive manipulation implemented in the task was found to be effective for both patients (t = 12.84, p < 0.001) and healthy controls (t = 11.13, p < 0.001), such that both groups selected the hard trial option more often during the high versus low value conditions.

The repeated-measures ANOVA model indicated significant main effects of probability (F_{2,228} = 204.0, p < 0.001) and reward value (F_{1,114} = 163.8, p < 0.001), with participants choosing the hard trial more often for trials with higher probability and reward value, respectively. There was also a significant interaction between probability and reward value (F_{2,228} = 11.4, p < 0.001). In terms of differences between groups, the ANOVA revealed a significant main effect of group (F_{1,114} = 20.4, p < 0.001), with patients with schizophrenia opting to expend greater effort at a significantly lower rate than healthy controls. Curiously, there was no interaction between group and probability (F_{2,228} = 0.02, p = 0.98), or group and reward value (F_{1,114} = 0.2, p = 0.66); however, there was a 3-way interaction between these variables (F_{2,228} = 4.0, p = 0.02; Figure 7-1A). Post-hoc one-way ANOVAs revealed a significant group difference in all trial types (all p's≤0.01; except the low-reward 10%-probability trials, p = 0.08), where patients with schizophrenia were found to be less willing to exert effort. Of note, the magnitude of group differences was larger for high value trials (90% trials, Cohen's d = 0.83) versus low value trials (10% trials, d = 0.57).
Figure 7-1. Performance on the reward processing variables for patients with schizophrenia and healthy control participants
(A) Performance on the effort-based decision making task. (B) Reward learning performance including of overall performance, and measures of rapid feedback-drive learning. (C) Mean self-reported pleasure ratings for various IAPS stimuli. Error bars denote standard error of the mean.

Overall, patients earned significantly less money compared to healthy subjects during the task ($t = 4.76, p < 0.001$). The amount of money won by patients was significantly correlated with total number of hard trials selected ($r = 0.82, p < 0.001$), especially for high value trials (i.e., 90%; $r = 0.78, p < 0.001$) rather than low value trials (i.e., 10%; $r = 0.35, p = 0.008$; difference: $z = 3.84, p < 0.001$). This variable, in particular, was examined in subsequent analyses given the greater correlation between high value trials and overall payout, as well as the greater magnitude of group differences.

During the post-task calibration trial, all participants executed at least the required number of button presses for the hard trial, ruling out the influence of fatigue or an inability to complete the hard trials during the task.

7.3.3 Simple Value-based Decision Making

Patients with schizophrenia performed significantly worse on the simple value-based decision making test ($t = 2.66, p = 0.009$). 68% of patients and 92% of controls demonstrated optimal and rational performance on this task, a significant difference in rates ($\chi^2 = 9.59, p = 0.002$).

The group difference in willingness to exert effort during high value trials remained in the subsample of participants with optimal performance on this task ($t = 4.32, p < 0.001$), suggesting that these effort impairments cannot fully be accounted for by pervasive decision making impairments or simple value-guided choice.
7.3.4 Reward Learning

Healthy control subjects demonstrated significantly better learning on the reinforcement learning task (t = 3.41, p = 0.001). Moreover, patients also demonstrated significantly poorer use of valid feedback to guide their subsequent choices; patients showed abnormal win-stay (t = 4.29, p < 0.001) and lose-shift choice behaviour (t = 2.6, p = 0.01). Specifically, patients were less likely to re-select a previously correct choice but, interestingly, were more likely to shift their selection following a previously incorrect choice. These results are graphically depicted in Figure 7-1B.

76.8% of patients and 86.2% of controls were classified as having intact reward learning capacity, defined as developing a preference for the most valued stimulus (or avoidance of the least valued stimulus). Patients were found to be less willing to expend effort for high value trials, even in the subsample of participants with intact reward learning capacity (t = 4.32, p < 0.001).

7.3.5 Hedonic Experience

The repeated measures ANOVA model revealed a significant effect of slide type (F_{2,228} = 224.9, p < 0.001; Figure 7-1C), and follow-up contrasts confirmed a significant linear effect (positive > neutral > negative; F_{1,114} = 403.3, p < 0.001). There was no significant main effect of group (F_{1,114} = 0.12, p = 0.73) or interaction between group and trial type (F_{2,228} = 0.02, p = 0.98), suggesting that the groups did not differ in the valuation of emotional stimuli.

As groups did not differ on this variable, there was no need to examine effort performance in patients with intact hedonic experience. Our subgroup analyses together demonstrate that in patients with schizophrenia a reduced willingness to expend effort for high value reward is not merely secondary to concurrent impairments in reward valuation, reward learning or simple decision making, suggesting an underlying impairment in the computation of effort costs.
7.3.6 A Multivariate Examination of Reward Processing Differences

Patients with schizophrenia had poorer performance on multiple, but not all, tests of reward processing. Among patients with schizophrenia, performance on these tasks was not highly correlated (Table 7-3). A multiple logistic regression model was constructed to examine which of these reward variables independently contributed to the observed group differences, whilst concurrently controlling for performance on the other variables. Reduced willingness to exert effort during high-value trials and poorer reward learning performance both independently predicted group membership, while hedonic experience (i.e., reward valuation) did not (Table 7-4); performance on the simple-value based decision making task was not a significant predictor, though a trend was noted. These results suggest that patients with schizophrenia concurrently evidence multiple impairments in reward processing, and that deficits in any one process cannot be fully accounted for by deficits in another.

Table 7-3. Inter-relationship between reward variables in patients with schizophrenia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effort cost computations</th>
<th>Reward valuation</th>
<th>Reward learning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effort cost computations(^a)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reward valuation(^b)</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reward learning(^c)</td>
<td>0.16</td>
<td>0.18</td>
<td>-</td>
</tr>
<tr>
<td>Simple value-based decisions(^d)</td>
<td>0.12</td>
<td>-0.14</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

\(^a\) Effort cost computation were indexed by the proportion of hard trials selected for high-value (i.e., 90% probability trials).

\(^b\) Reward valuation was evaluated using the mean valence rating for positive images.
Reward learning was evaluated as the proportion of higher value stimuli selected across stimulus-pairings during the reinforcement learning task.

Simple value-based decision making was indexed by a binary variable, optimal versus suboptimal, based on the selection of higher value options over lower value options.

Note: All reported correlations were non-significant (p > 0.10).

Table 7-4. Logistic regression analysis with reward processing variables predicting group membership

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wald's $\chi^2$</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effort cost computations$^a$</td>
<td>8.20</td>
<td>2.43</td>
<td>1.32 - 4.47</td>
<td>0.004</td>
</tr>
<tr>
<td>Reward valuation$^b$</td>
<td>0.00</td>
<td>1.00</td>
<td>0.64 - 1.56</td>
<td>0.98</td>
</tr>
<tr>
<td>Reward learning$^c$</td>
<td>4.40</td>
<td>1.70</td>
<td>1.04 - 2.78</td>
<td>0.04</td>
</tr>
<tr>
<td>Simple value-based decisions$^d$</td>
<td>3.74</td>
<td>3.37</td>
<td>0.98 - 11.55</td>
<td>0.053</td>
</tr>
<tr>
<td>Constant</td>
<td>2.83</td>
<td>0.38</td>
<td></td>
<td>0.09</td>
</tr>
</tbody>
</table>

$^a$ Effort cost computation were indexed by the proportion of hard trials selected for high-value (i.e., 90% probability trials).

$^b$ Reward valuation was evaluated using the mean valence rating for positive images.

$^c$ Reward learning was evaluated as the proportion of higher value stimuli selected across stimulus-pairings during the reinforcement learning task.

$^d$ Simple value-based decision making was indexed by a binary variable, optimal versus suboptimal, based on the selection of higher value options over lower value options.
Model statistics: $\chi^2 = 26.64$, df = 4, $p < 0.001$, Nagelkerke $R^2 = 0.306$; overall classification accuracy = 72.7%. Examination of multicollinearity statistics (e.g., variation inflation factor) did not reveal any violations of the assumptions of regression modeling.

Note: Model is predicting membership into the healthy control group. Higher odds ratios denote greater likelihood of being classified within the healthy control group versus the schizophrenia group. Predictor variables were standardized before analysis.

### 7.3.7 Association with Clinical Motivational Deficits, Other Clinical Variables, and Functional Outcome

Among the reward variables examined, only the effort variable significantly correlated with clinically-rated motivational deficits in patients with schizophrenia (Table 7-5). The relationship between effort and motivation is illustrated in Figure 7-2 using clinically-defined subgroups of patients, parsed based on the severity of motivational deficits. Importantly, effort performance was not related to a host of other clinical variables such as severity of depressive symptoms, positive psychotic symptoms, disorganization, extrapyramidal symptoms or negative symptoms related to diminished expression (all $p$'s > 0.05; Table 7-6). In addition, we did not find a relationship between effort and defeatist performance beliefs ($r = 0.11$, $p = 0.40$). Effort cost computations were, however, related to functional status ($r = 0.31$, $p = 0.02$) and, cognitive performance ($r = 0.31$, $p = 0.02$). To explore the independent relationships between cognition and motivational deficits on the one hand, and effort cost computations on the other, we constructed a multiple linear regression model with both of these variables predicting effort performance. This model revealed a significant relationship between motivation and effort cost computations ($\beta = -0.32$, $p = 0.02$; Model statistics: $R^2 = 0.17$, $F_{2,55} = 5.47$, $p = 0.007$), but once this association was accounted for no independent relationship was found between cognition and effort ($\beta = 0.16$, $p = 0.23$).

<p>| Table 7-5. Bivariate correlations between reward variables and clinical amotivation in schizophrenia |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effort cost computations&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.41</td>
<td>0.001</td>
</tr>
<tr>
<td>Reward valuation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.13</td>
<td>0.32</td>
</tr>
<tr>
<td>Reward learning&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.01</td>
<td>0.96</td>
</tr>
<tr>
<td>Simple value-based decisions&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-0.03</td>
<td>0.83</td>
</tr>
</tbody>
</table>

<sup>a</sup> Effort cost computation were indexed by the proportion of hard trials selected for high-value (i.e., 90% probability trials).

<sup>b</sup> Reward valuation was evaluated using the mean valence rating for positive images.

<sup>c</sup> Reward learning was evaluated as the proportion of higher value stimuli selected across stimulus-pairings during the reinforcement learning task.

<sup>d</sup> Simple value-based decision making was indexed by a binary variable, optimal versus suboptimal, based on the selection of higher value options over lower value options.

**Table 7-6. Bivariate correlations between the effort computation variable and selected clinical outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-0.14</td>
<td>0.30</td>
</tr>
<tr>
<td>Positive psychotic symptoms&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.24</td>
<td>0.07</td>
</tr>
<tr>
<td>Disorganization&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.09</td>
<td>0.49</td>
</tr>
<tr>
<td>Extrapyramidal symptoms&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-0.05</td>
<td>0.73</td>
</tr>
<tr>
<td>Expressive negative symptoms&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.22</td>
<td>0.09</td>
</tr>
</tbody>
</table>

<sup>a</sup> Depressive symptoms were evaluated using the total score from the Calgary Depression Scale for Schizophrenia.

<sup>b</sup> Positive psychotic symptoms were evaluated using the thought disturbance factor from the Brief Psychiatric Rating Scale.

<sup>c</sup> Symptoms of disorganization were evaluated using the disorganization factor from the Brief Psychiatric Rating Scale.

<sup>d</sup> Extrapyramidal symptoms were evaluated using the total score from the Simpson-Angus Scale.

<sup>e</sup> Expressive negative symptoms were evaluated using the sum score from selected items from the Scale for the Assessment of Negative Symptoms including items within the affective flattening subscale (excluding the global item) and the poverty of speech item from the alogia subscale.
We computed a repeated-measures ANOVA model for patients alone, including only probability as a within-subjects factor, and severity of motivational deficits as a covariate. This analysis revealed a significant interaction between probability and apathy severity ($F_{2,112} = 3.41, p = 0.04$). This interaction is illustrated in this graph, where patients with more severe apathy fail to increase the rate at which they make decisions to expend greater effort as the value of reward increases to similar extent as patients without prominent apathy. Error bars denote standard error of the mean. *$P < 0.05$. 

Figure 7-2. Effort performance for patients with schizophrenia stratified by severity of motivational deficits
Given the relationship between effort and functional outcome, as well as the relationship between effort and motivation independent of cognition, we were interested in whether clinical motivational deficits might mediate the relationship between effort cost computations on the one hand, and functional outcome (i.e., QLS-A scores) on the other. We tested this using mediation analysis (1215). First, effort was significantly related to functional outcome ($\beta = 0.28$, $p = 0.03$). Second, effort cost computations were associated with motivation ($\beta = -0.38$, $p = 0.003$). Motivation was also related to functioning scores ($\beta = -0.66$, $p < 0.001$). Finally, when both motivational deficits and effort cost were used to predict functional outcome, motivation emerged as a significant predictor ($\beta = -0.64$, $p < 0.001$) but effort did not ($\beta = 0.04$, $p = 0.73$). The Sobel's test was significant ($z = 3.06$, $p = 0.002$), demonstrating that motivation mediated the relationship between effort cost computations and functional outcome (Figure 7-3).

Figure 7-3. Mediation model, testing whether motivational deficits mediate the relationship between effort cost computations and functional outcome

The lines represent: (a) the direct effect of effort cost computations on motivation, (b) the direct effect of motivation on functional status, (c) the direct effect of effort cost computations on
functioning, and (c') the indirect effect of effort cost computations on functional outcome after parsing the contribution of motivational deficits. ***P < 0.001. **P < 0.01. *P < 0.05.

7.4 Discussion

There is increasing recognition of the importance of motivational deficits in schizophrenia, yielding various lines of investigations intent on uncovering underlying mechanisms. From a behavioural standpoint, inroads have been made in adapting paradigms from the pre-clinical behavioural neuroscience literature to isolate specific processes and applying these to patients. In the present study we sought to consolidate these lines of inquiry, and examine multiple reward processes in the same subjects. Our results revealed that individuals with schizophrenia demonstrate abnormalities in a number of these processes, including independent impairments in effort cost computations and reward learning in particular. The findings presented also replicate and extend some of our previous work (1221), specifically that patients with schizophrenia exhibit deficits in their willingness to expend effort for reward. This finding cannot be fully accounted for by other (concurrent) reward processing abnormalities, suggesting instead a specific impairment in the computation of effort demands, or possibly in the integration of this signal with subsequent processes. While several prior studies have explored whether effort-related choices are abnormal in patients with schizophrenia (904, 1221-1223, 1243, 1255-1258), most have been limited by the inclusion of a single task (i.e., evaluation of only one reward process), thus precluding any inference around specific computational abnormalities (i.e., presence of specific impairments in effort costs computations). Our study distinctively advances this area by providing evidence for such a computational deficit.

Beyond group differences between patients and controls on reward processing variables, we also explored the relationship between these variables and individual differences in clinically-rated motivational deficits in individuals with schizophrenia. Of the reward variables, only willingness to expend effort for high-value rewards (i.e., our index of effort cost computations) was found to be correlated with severity of amotivation. Notably, the magnitude of this relationship was not extremely large, which is in keeping with previous work (1223, 1248, 1259). We have argued elsewhere that this might reflect differences in the nature and focus of the assessment strategies, with task-based assessments tapping into a specific computational process, whereas clinical
ratings reflect an amalgamation of sources of variance that could each undermine motivated behaviour in the real-world, including environmental constraints (1248). We also found a relationship between effort performance and functional status, suggesting a role for these computational processes in predicting outcomes in this illness. To explore this issue further, we conducted a mediation analysis and found that severity of clinical motivational deficits mediated the relationship between effort computations and outcome. As an aside, it is important to note that our measure of motivational deficits (i.e., the AES-C) evaluates motivation mainly from a subjective standpoint, thereby minimizing conceptual overlap with measures of functional outcome (891). At any rate, our results provide a theoretical framework for understanding at least one path that can potentially undermine functional recovery among patients with (early) schizophrenia. That is, underlying impairments in patients' ability to compute and integrate the effort demands required in executing actions in pursuit of valued outcomes serves as at least one contributor to the manifestation of clinical (subjective) reductions in drive and initiative (i.e., amotivation). In turn, these subjective motivational deficits undermine patients' behaviour in the real-world, which results in poorer social networks and underproductive vocational functioning.

Impairments in motivation and community functioning are certainly an area of clinical concern, both representing unmet therapeutic needs. Outside of the computational and mechanistic implications of our effort findings, these results also provide important clinical information. Many patients with schizophrenia, including those included in the present study, evidence poor psychosocial functioning even in the early stages of illness (874, 891, 1200). Patients often decline rehabilitation programs, or their involvement in such programs is undermined by their motivational impairments (1241). State-of-the-art care has shown some benefits in terms of improving these domains, but impairments remain in different facets of real-world functioning for the majority of patients (177, 285). Our results, using a performance-based assessment, echo this reality; we demonstrate that even within a controlled laboratory setting patients are generally less willing to work in exchange for promised reward, even if they value the reward (i.e., money). Such performance-based measurements of effort and motivation have the potential to serve as viable endpoints in clinical trials addressing negative symptoms and motivational deficits, as these paradigms might be tapping into underlying impairments in a fashion that broad interview-based assessments of motivational deficits are not.
Cognitive performance was also found to correlate with effort performance; patients who expended greater effort during the effort-based decision making task performed better on standard neurocognitive measures. However, when examined in conjunction with motivational deficits, it was found that cognition did not demonstrate a relationship with effort performance over and above the inter-relationship between motivation and the latter. One explanation for this finding is that the portion of variance between cognitive performance and effort is also related to motivation (i.e., overlapping variance between motivation and cognition). Several previous studies employing standard neuropsychological performance validity tests as measures of effort have shown that (cognitive) effort measured in this manner is significantly related to cognitive test performance (1131, 1132, 1227, 1260). This has been taken as evidence by some to indicate that a portion of the variance being measured by cognitive tests may reflect a motivational influence. In fact, we have previously found that patients' self-reported motivation to complete cognitive testing procedures is significantly associated with their performance on those same cognitive tests (1216).

We did not find a relationship between defeatist performance beliefs and effort performance. This is in keeping with one previous study reporting on such a relationship, or lack thereof as the case might be (1259). A lack of relationship is somewhat surprising given several findings of a significant relationship between these dysfunctional attitudes and motivational deficits (832, 833, 839, 1261), though conflicting evidence also exists (855). In contrast, a recent study, using pupillary responses as an index of effort, reported a relationship between this variable and defeatist performance beliefs (1262); specifically, patients with the highest defeatist beliefs deployed significantly less effort during high cognitive demands relative to patients who endorsed only mild defeatist beliefs. However, we should note that in the present sample of early-course patients, defeatist beliefs were not associated with severity of motivational deficits, expressive negative symptoms or functional status (all p's>0.05), though patients did endorse greater defeatist beliefs compared to healthy controls.

Our study has several strengths that bolster confidence in our findings. We recruited a relatively selective sample of patients with schizophrenia, only including young early-course patients without prominent depression or medication-related side effects. This is important, as these other variables may influence performance on reward tasks. For instance, one previous study found that patients with greater total negative symptoms exerted less effort during a decision making
task than patients with lower levels of total negative symptoms, though an association with motivational deficits in particular was not found (904). A subsequent re-analysis of these data revealed that these findings may be have unduly influenced by the inclusion of patients receiving first-generation antipsychotic medications, as the exclusion of this group nullified the observed relationship between negative symptoms and effort performance (1263). As such, our inclusion of patients receiving atypical antipsychotic monotherapy minimizes such iatrogenic confounds in the assessment of reward processing and motivation in patients with schizophrenia. It should also be noted that all patients included in the present investigation were deemed competent to provide informed consent as per the MacCAT, which evaluates patients' ability to understand and appreciate information provided to them, as well as reason and make an informed decision. This means that all included participants were able to understand the constraints of their participation in the study, reason about the potential benefits and risks associated with participating, and make a rational decision that integrates their understanding of the study information. In other words, all patients' were able to orient and attend to the presented information, and were not severely disoriented or disorganized such that they could not evaluate or integrate presented information. Even in the face of the absence of such gross "decision making capacity" deficits, it is notable that patients still evidenced impairments in reward-driven decision making. Another strength of our study is the exclusion of patients with co-morbid or concurrent psychiatric disorders, including for example obsessive-compulsive disorder, which itself has been associated with reward processing and decision making abnormalities (1264).

In evaluating the results of the present study, some potential limitations should be mentioned. While several selected reward variables were examined in the present study others were not (e.g., habit learning), and so it remains possible that other processes may also, perhaps independently or through interactions, predict the burden of motivational deficits in patients with schizophrenia. Another limitation involves the use of single tasks to evaluate reward processing constructs, and as such the assessments are contaminated by task-specific measurement variance. We point out, though, that most of the variables examined used a summary score incorporating multiple responses. For example, the effort variable for the high-value 90%-probability trials includes responses to low and high monetary value bins, and the reward learning variable includes performance on 3 different stimulus-outcome pairings. As mentioned above, we included a selected sample of patients with schizophrenia that excluded different subgroups (e.g., severely
ill inpatients). The generalizability of our findings to these other populations therefore remains to be established.

The present findings demonstrate that patients with schizophrenia are impaired in the processing of reward information, including the ability to use this information to rationally guide decision making. We found evidence for the existence of effort computation impairments, a finding that remained after taking into account concurrent impairments in stimulus-outcome learning and preference-guided choice. Moreover, the clinical importance of effort computation impairments was underscored by their significant associations with motivational deficits and functional outcome. We argue that these impairments contribute to the clinical manifestation of apathetic behaviour, which in turn undermines opportunities for functional recovery in patients with schizophrenia. Our findings, involving relatively young adults early in the course of their illness, highlight that these impairments manifest soon after illness onset, if not before. Identifying and targeting these deficits early offers the potential to curb prospective functional impairments and associated burden, while a greater understanding of mediating factors and/or neurobiological substrates may provide an avenue of research that can identify viable (intermediate) targets that have the potential to engage the computational processes in question.
8 Effort-based Decision Making as an Objective Paradigm for the Assessment of Motivational Deficits in Schizophrenia

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8.1 Introduction

Negative symptoms are a prevalent feature of schizophrenia (822), for which there are no currently effective treatments (271). The importance of negative symptoms is underscored by consistent findings across studies suggesting that they represent a critical barrier to patients' ability to achieve functional recovery (485, 660, 838, 851). Of the broad array of negative symptoms observed among patients with schizophrenia, symptoms related to amotivation have emerged as particularly important predictors of poor functional outcome (679, 839, 845, 850, 876, 891).

Despite the functional burden of these symptoms, our understanding of the mechanisms underlying amotivation remains incomplete. Further, current "gold standard" methods of evaluating motivational deficits rely on clinical ratings usually based on patient self-report (573, 1265). Recently, several studies have employed performance-based tasks to objectively demonstrate effort-related motivational deficits in patients with schizophrenia (904, 1221-1223, 1243, 1255, 1256). Specifically, these studies demonstrate that within a controlled laboratory
setting patients are generally less willing to expend effort in pursuit of reward compared to matched healthy volunteers. The use of performance-based assessment tools to capture motivational deficits offers several advantages, such as the ability to evaluate these symptoms relatively free of external biases that can potentially undermine community functioning (e.g., availability of resources) (1266). Importantly, performance on these tasks has been associated with severity of motivational impairment and functional status (1221-1223).

Another potential advantage of certain performance-based assessments of amotivation is the existence of analogous paradigms for use pre-clinically, effectively setting the stage for translational investigations (493, 881). Future studies may evaluate potential pro-motivation interventions both in humans and other species using such paradigms. It may well be the case that these laboratory-based assessments of motivation, which have been linked to specific neural circuits (881), are more sensitive to treatment response. This may be the case as real-world impairments are typically multifactorial, being (putatively) caused by impairments in neural processes as well as situational factors. For instance, patients may lack engagement within the community due to their impaired ability to process environmental cues (i.e., neural processing), but also because of stigma, lack of opportunity, or lack of support (i.e., situational factors). Utilizing a translational objective paradigm akin to those used pre-clinically may represent a strategy with stronger links between circuit functioning and behaviour, as situational factors are minimized in this context. There are several lines of investigation to support this position; for example, single doses of amphetamine have been found to increase effort expenditure in pursuit of reward among healthy controls (1008), a finding that mirrors pre-clinical work in rodents (974). However, amphetamine has not produced substantial effects on clinically rated negative symptoms in patients with schizophrenia (1267, 1268).

In the present study we sought to examine the psychometrics of an effort-based decision making task, including metrics to evaluate the utility of such an assessment in the context of repeated measurements. We focus on effort-based decision making as a novel translational paradigm evaluating effort-related motivational deficits (881). Establishing the psychometrics of an objective performance-based assessment of motivational deficits in patients with schizophrenia serves as an important first step in determining whether such a paradigm might have utility in the context of clinical trials evaluating the efficacy of potential treatments. In order to serve this
purpose, a task should be sensitive to manipulation effects, have high test-retest consistency, and demonstrate minimal practice effects, amongst other desirable characteristics (1269).

8.2 Methods

8.2.1 Participants

Patients with schizophrenia were recruited from outpatient clinics at the Centre for Addiction and Mental Health in Toronto, Ontario, Canada. Selection criteria for participants included: (1) diagnosis of a schizophrenia spectrum disorder, confirmed using the Mini International Neuropsychiatric Interview (1193), (2) age 18-65 years, (3) competence to provide informed consent, evaluated using the MacArthur Competence Assessment Tool (1228), (4) no serious or unstable medical condition, and (5) ability to communicate in English. The study was approved by the institutional research ethics board, and all participants provided written informed consent prior to study participation.

8.2.2 Instruments and Procedure

This study involved three visits on different days within one month. The first visit included clinical assessments, and during the next two visits participants completed the effort-based decision making task. These latter two visits were conducted 2 weeks apart. Participants received a fixed amount of monetary compensation at the end of each study visit for their participation in the present study. During the first visit, psychopathology was evaluated using the 18-item Brief Psychiatric Rating Scale (BPRS) (556), and the self-report version of the Apathy Evaluation Scale (AES) (692). Neurocognition was evaluated using the Brief Neurocognitive Assessment for Schizophrenia (1245, 1246).

The effort-based decision making task used in the present study represents a modified version of the Effort Expenditure for Rewards Task (1006). Briefly, this represents a multi-trial game that assesses participants' willingness to expend effort for monetary reward. On each trial, subjects choose to complete an "easy" or "hard" trial (Figure 8-1). For an easy trial, subjects must use the index finger of their dominant hand to press the L-key (on a standard keyboard; S-key for left-
handed individuals) a set number of times within 10 seconds to win $1.00. For hard trials, participants must use the pinky finger of their non-dominant hand to press the S-key (L-key for left-handed individuals) a set number of times also within 10 seconds to win $1.50-6.00. The easy trial was always worth $1.00, whereas there were 10 possible values for the hard trial option ranging from $1.50 to $6.00 in $0.50 increments. Probability of receiving reward was also varied at 3 levels, and each reward magnitude for the hard trial option was presented once for each probability level, resulting in a total number of 30 trials. The version of the task used in the present study includes several modifications compared with the original paradigm (1006). These modifications include: (1) equalization of the duration of each trial, thus nullifying decision costs related to temporal delay; (2) fixed number of 30 trials, with a brief break mid-way through the task; (3) use of rounded values for probability (i.e., 10%, 50%, and 90%) and monetary reward (e.g., $3.00, $3.50, $4.00); and (4) calibration of the requisite number of button presses. To this last point, before beginning the task, participants' maximum button pressing rate for their non-dominant hand was evaluated across 3 trials where they were instructed to press the respective key as many times as possible (1221). The highest value across the 3 trials was used as the maximum rate, and the button press criterion for easy and hard trials was based on this personalized value. Specifically, the hard task required 80% of the subject's calculated maximum rate, whereas the easy task required half this number. Before the actual task, participants completed 4 practice trials to ensure familiarity and comprehension of the task. The primary outcome variable was proportion of trials where participants selected the hard trial option. Participants were instructed to perform as if they were playing for "real" rewards, however the monetary rewards were fictional, meaning that participants did not actually receive performance-contingent payments; that the rewards were hypothetical was described to participants before they completed the task. In the instructions, the task was described as a button-pressing game, and participants were not explicitly told that the task was evaluating motivation. The task was executed in MATLAB R2009b (Mathworks Inc., Natick, MA) using PsychToolbox (1249) running in Windows.
Figure 8-1. Diagram depicting the sequence of a single trial of the effort-based decision making task

Trials begin with a fixation cue. Then, during the decision-phase, subjects are presented with reward magnitude information for the easy and hard trial options as well as the probability of receiving reward. Once subjects make a decision to complete an easy or hard trial, they are shown a screen prompting them to get ready for the respective trial. Participants were given up to 7 seconds to make a decision, and if they did not make a decision within this timeframe, they proceeded to the easy trial option. During the actual effort trial, participants made button presses for an individually determined number of times within 10 seconds to complete the task. For this portion, subjects could track their progress through an illustrative bar which progressively filled after each individual button press, with the top indicating completion of the task. If participants completed the task before an elapsed trial time of 10 seconds, participants were asked to wait until the full trial time had elapsed. Participants were shown a counter in the top right-hand corner of the screen which displayed the amount of time remaining for each trial. Next, an outcome screen was presented, providing feedback as to whether the trial was successfully completed and if so, the amount of monetary winnings were also presented.
Directly following task administration, participants completed another calibration run with their non-dominant pinky finger to evaluate potential fatigue effects. Participants next completed a questionnaire regarding the task and testing procedures. Participants were asked to rate the level effort/difficulty of the easy and hard trials on an 11-point Likert scale with scores ranging from 0 (not at all difficult) to 10 (extremely difficult). As an index of tolerability, participants were also asked to rate how difficult they found the task overall using the same Likert scale. In addition, participants were also asked whether they were driven to perform well and win money during the task.

8.2.3 Statistical Analyses

Whether the task was effective in having participants expend effort for reward was evaluated by examining incentive effects. Specifically, we evaluated whether participants were more likely to select hard trials for the higher value trials (indexed by the 90% probability condition) versus lower value trials (indexed by the 10% probability condition). We also examined the effect of probability and reward level on effort expenditure using a 3-by-2 repeated-measures analysis of variance (ANOVA) model. Reward values were binned into large and small values following a median split; specifically, monetary rewards of $4 or greater were classified as large.

Beyond the examination of incentive effects, the main outcome measure for the remaining analyses was the proportion of hard trial options selected across the entire task. Our decision to examine this "composite" effort score was guided by several factors. First, we decided not to examine effort expenditure for each reward value and probability condition separately to reduce the sheer number of statistical tests, and thereby reduce inflation of Type I errors; however, these values were used in specific analyses (e.g., relationship with negative symptoms). Second, we found that effort expenditure within these different bins were highly correlated (3 probability levels and 2 reward levels results in a total of 6 bins; correlation range = 0.36-0.80, all p's < 0.001). Furthermore, a principal components analysis with varimax rotation revealed a clear single factor solution that explained 72.0% of the variance; all variables loaded highly onto this component, each with loadings greater than 0.76. The internal consistency of this composite measure was found to be excellent (Cronbach's α = 0.90). For these reasons, we used the total number of hard (i.e., high effort) trials selected as our outcome variable.
Test-retest reliability of the effort task was evaluated using intraclass correlation coefficients (ICCs), and mean change in scores over time (i.e., practice effects) were quantified using paired-samples t-tests; effect size was calculated by dividing the mean difference score by the standard deviation of the change scores. We also re-examined the test-retest reliability and mean change in scores over time in a subgroup of participants with greater severity of motivational deficits as defined as a score of 34 or greater on the AES. This score was selected based on normative data from a healthy control sample where this cut-off represented a score that was greater than 2 standard deviations above the mean score for a healthy adult sample (1254), an approach that has been used in other studies (874). This cut-off score represents a score that is greater than both the median and mean AES values for the present sample of patients with schizophrenia.

Finally, we examined whether task performance during the initial testing session was associated with clinical variables such as severity of psychopathology using Pearson's product-moment correlation coefficients. Neurocognition scores were transformed to age- and sex-matched Z-scores based on normative data (1246). Discrete aspects of psychopathology such as positive and negative symptom severity was evaluated using factor scores derived from the BPRS (1229), while severity of overall symptoms was quantified using the total score from the BPRS. In addition, we explored whether there was any significant relationship between task performance and antipsychotic dosage (i.e., chlorpromazine equivalents)(1231). Beyond associations with quantity of antipsychotic medications, we were also interested in potential associations with antipsychotic type or class. To this end, patients receiving typical antipsychotic medications either alone or in combination with atypical agents were compared to patients receiving atypical antipsychotic medications only. Further, we also examined whether there was any difference in task performance for participants receiving different antipsychotic medications. For this, we included a particular antipsychotic medication in our analysis if a reasonable number of participants were receiving monotherapy with the antipsychotic in question. We included the following three medications: clozapine (N = 20), olanzapine (N = 14), and a combined group of risperidone and paliperidone (N = 16). Groups were compared using a one-way ANOVA model.

We also examined potential group differences in effort performance in patients classified as having the deficit subtype of schizophrenia using the proxy case identification method (1270). Specifically, the proxy for the deficit syndrome was defined as the sum of the anxiety, guilt feelings, depressive mood and hostility items of the BPRS, subtracted from the blunted affect...
score. A cut-off point of -2 was used to classify deficit versus nondeficit cases (1270); those with a score of -3 were considered ambiguous cases and excluded from analyses.

Statistical tests were considered significant at a p-value of less than 0.05 (two-tailed). Data were first processed using custom written scripts in MATLAB, and subsequently exported to SPSS Statistics version 20 (IMB Corp., Armonk, NY, USA) for statistical analyses.

8.3 Results

8.3.1 Patient Characteristics

Ninety-nine patients with schizophrenia spectrum disorders participated in the present study. Data from 2 participants was discarded as they made decisions on less than 20% of trials. Therefore, the final sample comprised of 97 patients with schizophrenia spectrum disorders. Sociodemographic and clinical characteristics of the sample are presented in Table 8-1. Ninety-two patients completed the effort task during the retest session. These patients did not differ from the participants who did not complete the second iteration of the effort task on any sociodemographic or clinical variable (all p's > 0.05). Moreover, repeating the analyses including only the 92 patients with data from both testing sessions revealed essentially identical results.

Table 8-1. Sociodemographic and clinical characteristics of the patient sample (N = 97)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (S.D.) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.4 (11.4)</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>59.8</td>
</tr>
<tr>
<td>Handedness (% right-handed)</td>
<td>92.7</td>
</tr>
<tr>
<td>Age at first hospitalization (years)</td>
<td>24.3 (7.6)</td>
</tr>
<tr>
<td>Duration since first hospitalization (years)</td>
<td>15.6 (11.2)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Current cigarette smokers (% yes)</td>
<td>42.2</td>
</tr>
<tr>
<td>Weight (kilograms)</td>
<td>92.2 (22.1)</td>
</tr>
<tr>
<td>Body mass index (kilograms/meters²)</td>
<td>31.6 (7.7)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>61.9</td>
</tr>
<tr>
<td>Black</td>
<td>14.4</td>
</tr>
<tr>
<td>Other</td>
<td>23.7</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>62.9</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>36.1</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
</tr>
<tr>
<td>Antipsychotic type (%)</td>
<td></td>
</tr>
<tr>
<td>Atypical only</td>
<td>76.3</td>
</tr>
<tr>
<td>Typical only</td>
<td>10.3</td>
</tr>
<tr>
<td>Atypical and typical combination</td>
<td>10.3</td>
</tr>
<tr>
<td>None</td>
<td>3.1</td>
</tr>
<tr>
<td>Antipsychotic dosage (chlorpromazine) equivalents</td>
<td>5202.8 (312.6)</td>
</tr>
<tr>
<td>BPRS Total</td>
<td>35.1 (8.5)</td>
</tr>
<tr>
<td>BPRS Positive symptoms</td>
<td>8.8 (4.6)</td>
</tr>
<tr>
<td>BPRS Negative symptoms</td>
<td>7.5 (3.4)</td>
</tr>
</tbody>
</table>
AES Total 32.1 (8.1)
Global cognition standardized Z-score (BNA) -1.3 (1.3)

Abbreviations: AES: Apathy Evaluation Scale; BPRS: Brief Psychiatric Rating Scale; BNA: Brief Neurocognitive Assessment.

8.3.2 Task Performance

Participant's maximum button press rate with their non-dominant hand was 48 presses (SD = 11); this rate was not associated with their decisions to expend effort ($r = 0.08$, $p = 0.45$). On average, for the hard trial option participants were required to repeatedly press a button 39 (SD = 9) times, whereas only 20 (SD = 5) presses were required for the easy trial option.

The incentive manipulation was found to be effective, as participants selected the hard trial option more often during the high versus low value condition ($t_{96} = 5.68$, $p < 0.001$). Participants made decisions to expend effort for 96% of trials (SD = 7%), and only 3 participants had decision rates lower than 80%, notwithstanding the two excluded participants. Patients completed 97% of trials (SD = 5%), with the vast majority completing more than 90% of trials; only one participant completed less than 80% of trials.

The repeated-measures ANOVA model indicated significant main effects of probability ($F_{2,192} = 23.49$, $p < 0.001$) and reward value ($F_{1,96} = 14.22$, $p < 0.001$), with participants choosing the hard trial option more often for trials with higher probability and reward value, respectively. There was also a significant interaction between probability and reward ($F_{2,192} = 6.19$, $p = 0.002$). Follow-up repeated-measures ANOVA models computed separately for high and low reward values revealed that while the likelihood of hard choices increased from the low to medium ($F_{1,96} = 13.99$, $p < 0.001$) and medium to high probability levels ($F_{1,96} = 15.08$, $p < 0.001$) for the low reward values, there was a significant increase from low to medium probability levels ($F_{1,96} = 35.84$, $p < 0.001$) but not from the medium to high probability levels ($F_{1,96} = 0.40$, $p = 0.53$) for the high reward values. Moreover, separate repeated-measures ANOVA models computed for
each probability level separately, indicated that reward value had a significant effect of choice for the low ($F_{1,96} = 8.11, p = 0.005$) and medium ($F_{1,96} = 23.91, p < 0.001$) probability levels, but not for the high probability trials ($F_{1,96} = 0.57, p = 0.45$). These data are reported in Table 8-2, and graphically depicted in Figure 8-2.

### Table 8-2. Proportion of hard trials selected on the effort task

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mean proportion of hard trials selected (S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.57 (0.03)</td>
</tr>
<tr>
<td><strong>Probability</strong></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>0.47 (0.04)</td>
</tr>
<tr>
<td>50%</td>
<td>0.61 (0.03)</td>
</tr>
<tr>
<td>90%</td>
<td>0.64 (0.03)</td>
</tr>
<tr>
<td><strong>Reward value</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.52 (0.03)</td>
</tr>
<tr>
<td>High</td>
<td>0.63 (0.03)</td>
</tr>
<tr>
<td><strong>Probability x Reward</strong></td>
<td></td>
</tr>
<tr>
<td>10% probability</td>
<td></td>
</tr>
<tr>
<td>Low reward value</td>
<td>0.43 (0.04)</td>
</tr>
<tr>
<td>High reward value</td>
<td>0.50 (0.04)</td>
</tr>
<tr>
<td>50% probability</td>
<td></td>
</tr>
</tbody>
</table>
Low reward value: 0.55 (0.04)
High reward value: 0.67 (0.04)

90% probability and low reward value
Low reward value: 0.63 (0.03)
High reward value: 0.65 (0.04)
Figure 8-2. Mean proportion of hard trials selected as a function of reward value and probability level

Monetary reward for the hard trial option between $1.50 and $3.50 were classified as small, whereas reward values between $4.00 and $6.00 were classified as large.

8.3.3 Utility as a Repeated Measure

The primary outcome measure of proportion of hard trials selected demonstrated good consistency across time (ICC = 0.72). Moreover, performance during the 2 testing times was not found to be significantly different from one another, though a trend towards statistical significance was noted ($t_{91} = 1.88, p = 0.06$). The effect size of the change scores was 0.20, with participants selecting the hard trial option less often during the second testing session versus the first. Twelve participants (13%) had scores at ceiling during the first testing session, and excluding these participants resulted in slightly better psychometric properties. Specifically, the test-retest consistent was higher (ICC = 0.77), and the change in scores over time was lower (effect size = 0.05; $t_{79} = 0.45, p = 0.66$). These participants who invariably selected the hard trial option throughout the task were found to have more severe psychotic symptoms ($t_{90} = 2.91, p = 0.005$), but did not differ with respect to severity of other symptoms or cognitive impairment (all $p$'s > 0.05).

Next, we re-examined these test-retest metrics in a subgroup of patients with greater severity of motivational deficits (after also removing participants who scored at ceiling on the effort task during the first test session; $N = 33$). Even in this subgroup of participants, the main outcome measure of proportion of hard trials selected demonstrated good consistency across time (ICC = 0.71), and there was minimal change in scores over time, with participants selecting the hard trial option slightly more often during the second testing session versus the first (effect size = 0.08; $t_{32} = 0.45, p = 0.66$).
8.3.4 Fatigue Effects

Participants were asked to repeat the calibration run after the effort task, in order to evaluate whether they were able to complete the requisite number of hard presses. During this post-task run, all but one participant exceeded the requisite number of button presses; the one participant who did not exceed this number, executed only 2 fewer button presses than the number required to complete the task. This suggests that all participants were indeed able to expend the effort required for the hard trial option, meaning that decisions to expend less effort cannot be attributed to fatigue effects.

The mean task administration time including instructions, practice trials, and the mid-way break was 18 minutes (SD = 3). The actual experimental trials took approximately 11 minutes to complete.

8.3.5 Post-task Questionnaire

Participants found the hard trial significantly more effortful and difficult than the easy trial option ($t_{69} = 8.62, p < 0.001$; mean rating for easy trial = 2.0, SD = 2.5; mean rating for hard trial = 5.5, SD = 2.8). Considering the task overall, the mean difficulty rating was 4.0 (SD = 2.5), suggesting that on average participants did not find the overall task and testing procedures overly difficult. Also, on average participants were driven (i.e., motivated) to perform well on the task (mean rating = 7.3, SD = 2.5; a rating of 10 indicates extremely driven).

8.3.6 Association with Sociodemographic and Clinical Variables

Task performance was not associated with participants age ($r = -0.17, p = 0.10$) or sex ($t_{95} = 0.85, p = 0.40$). Duration since patients' first hospitalization was similarly not related to decisions to expend effort during the decision making task ($r = -0.19, p = 0.11$). Effort task performance was also not related to current cigarette smoking status ($t_{88} = 0.97, p = 0.33$), participants' weight ($r = 0.05, p = 0.66$), or their body mass index ($r = -0.03, p = 0.80$). Moreover, participants with a diagnosis of schizophrenia did not differ in their decisions to expend effort on the task from participants with a diagnosis of schizoaffective disorder ($t_{94} = 0.63, p = 0.53$). Task performance
was also not associated with severity of positive symptoms \( r = 0.16, p = 0.11 \) or with severity of overall symptoms \( r = 0.11, p = 0.27 \). Willingness to expend effort for reward was also not related to cognitive functioning \( r = 0.17, p = 0.13 \).

There was also no relationship between antipsychotic dosage and task performance \( r = 0.15, p = 0.16 \). Moreover, patients receiving typical antipsychotic medications did not differ from patients receiving atypical antipsychotics only \( t_{92} = 0.85, p = 0.40 \). In addition, we also explored whether effort performance differed between participants on specific antipsychotic medications. Participants receiving clozapine, olanzapine, or risperidone/paliperidone did not differ in terms of age, antipsychotic dosage, or severity of clinical symptoms \( \text{all } p's > 0.14 \). Participants receiving different medications also did not differ in their decisions to expend effort on the task \( F_{2,47} = 1.51, p = 0.23 \). To further examine whether these groups might have differed in their pattern of effort expenditure, we included medication as a between-groups factor into the repeated-measures ANOVA model. This model failed to reveal a significant main effort of medication or any significant interaction term with medication group \( \text{all } p's > 0.13 \). This suggests that the relative pattern of responding is similar across groups.

Contrary to expectations, task performance was not associated with self-rated motivational deficits on the AES \( r = 0.07, p = 0.47 \) or clinician-rated negative symptoms on the BPRS \( r = -0.09, p = 0.37 \). We also examined the relationship between motivational deficit and negative symptom ratings with the proportion of hard trials selected for each probability level, high and low reward levels, for reward levels stratified by probability, and for the difference in proportion of hard trials selected during the highest and lowest probability levels. None of these associations were statistically significant \( \text{all } p's > 0.05 \). Next, we explored whether patients' self-reported motivation to perform well was related to task performance; patients who reported a greater drive to perform well were more likely to exert effort for reward \( r = 0.36, p = 0.002 \).

### 8.3.7 Effort Performance in the Deficit Syndrome

Twelve patients were classified as having the deficit syndrome. These patients had more severe negative symptoms than nondeficit patients, but did not differ in terms of positive symptom severity disorganized symptoms, or antipsychotic dosage (Table 8-3). In addition, deficit patients experienced significantly less affective symptoms. These clinical characteristics support the construct validity of the deficit syndrome classification \( 520 \). Deficit schizophrenia patients
were found to expend effort for reward significantly less than nondeficit patients ($t_{90} = 2.19$, $p = 0.03$; Figure 8-3).

### Table 8-3. Characteristics of the patient sample stratified by deficit syndrome status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deficit Schizophrenia (N=12)</th>
<th>Nondeficit Schizophrenia (N=80)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.9 (13.4)</td>
<td>40.3 (11.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>75.0</td>
<td>57.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS Total</td>
<td>33.8 (8.1)</td>
<td>35.7 (8.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>BPRS Positive symptoms</td>
<td>8.6 (4.6)</td>
<td>9.1 (4.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>BPRS Negative symptoms</td>
<td>11.3 (4.1)</td>
<td>6.9 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPRS Affective symptoms</td>
<td>6.8 (1.6)</td>
<td>12.3 (3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPRS Disorganized symptoms</td>
<td>4.8 (2.1)</td>
<td>4.6 (1.9)</td>
<td>0.72</td>
</tr>
<tr>
<td>AES Total</td>
<td>29.4 (8.9)</td>
<td>32.8 (7.9)</td>
<td>0.17</td>
</tr>
<tr>
<td>Global cognition standardized Z-score (BNA)</td>
<td>-1.1 (1.7)</td>
<td>-1.3 (1.3)</td>
<td>0.68</td>
</tr>
</tbody>
</table>
Antipsychotic dosage (chlorpromazine) equivalents

| Antipsychotic dosage (chlorpromazine) equivalents | 406.6 (213.8) | 546.7 (321.8) | 0.17 |

Task variables

<table>
<thead>
<tr>
<th>Task variables</th>
<th>Easy trial difficulty</th>
<th>Hard trial difficulty</th>
<th>Overall task difficulty</th>
<th>Drive to perform well</th>
<th>Maximum button-press rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy trial difficulty</td>
<td>3.4 (2.9)</td>
<td>5.4 (2.8)</td>
<td>0.13</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>Hard trial difficulty</td>
<td>6.6 (3.5)</td>
<td>5.4 (2.8)</td>
<td>0.32</td>
<td>0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>Overall task difficulty</td>
<td>5.1 (3.4)</td>
<td>3.9 (2.4)</td>
<td>0.21</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>Drive to perform well</td>
<td>6.4 (4.0)</td>
<td>7.4 (2.3)</td>
<td>0.33</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>Maximum button-press rate</td>
<td>44.0 (10.9)</td>
<td>48.9 (11.6)</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Abbreviations: BPRS: Brief Psychiatric Rating Scale; AES: Apathy Evaluation Scale; BNA: Brief Neurocognitive Assessment.

a Based on independent samples t-tests all variables except sex, for which the χ² statistic was computed.

b The difficulty for the hard trial option was greater than that for the east trial option based on paired-samples t-tests (p < 0.05).
Figure 8-3. Willingness to expend effort for reward for deficit versus nondeficit schizophrenia patients

We were further interested in potential differences in the pattern of effort expenditure between deficit and nondeficit patients. For this, we included deficit syndrome status as a between-groups factor into the repeated-measures ANOVA model. This model failed to reveal any significant interaction term with deficit status (all p's > 0.25), but did reveal a significant main effect of deficit syndrome status ($F_{1,90} = 4.60, p = 0.04$). This suggests that the relative pattern of responding is similar across groups but that deficit patients expend effort significantly less for all reward values.
8.4 Discussion

The present investigation sought to examine the validity and reliability of a performance-based assessment of motivation deficits in patients with schizophrenia. We evaluated an effort-based decision making task as a specific measure of effort-related motivational impairment. Performance on this task was sensitive to manipulation effects such that patients increased their likelihood to expend effort when rewards were greater in value or their receipt was more probable. These results are consistent with previous work (904, 1221, 1223, 1243), but also extend the findings from these previous studies. Specifically, we show the effort task is valid, and that patients are able to modulate effort-related choice based on reward information even in the absence of tangible rewards. This suggests that participants are able to comply with task instructions and are on average reasonably motivated to perform well on the task.

While patients did demonstrate significant incentive effects, and did modulate their choice behaviour based on reward value and probability, we did also find a significant reward by probability interaction. This was qualified by the finding that patients did not choose to expend effort at a differential rate between the 50% and 90% probability conditions for high value rewards (Figure 8-2). That is, patients did not choose to expend effort for high-value high-probability rewards at a rate that was higher than their choice to expend effort for uncertain high-value rewards. This is especially noteworthy given findings from previous studies demonstrating that patients with schizophrenia expend effort for these high-value trials at a significantly lower rate than healthy controls (904, 1221, 1223, 1256). In the present study, patients as a group opted to work for high-value rewards less than 65% of the time, a value that is far from ceiling suggesting that patients' lack of effort cannot be ascribed to an already high rate of effort expenditure. This finding is consistent with our previous work using a different effort-based decision making task, where we found that patients chose to work for high-value high-probability trials less than 60% of the time, whereas healthy controls chose to expend effort more than 80% of the time for such trials (1221). It is also consistent with other studies where patients' have been found to expend effort for high value trials at a rate of less than 70% (904, 1223, 1256). It will be important going forward to ascertain means to enhance this rate of engagement in effortful behaviour in pursuit of valued outcomes as this could very well be exploited for the treatment of these deficits.
Effort performance was found to be stable and consistent over 2 testing sessions. The level of longitudinal consistency is comparable to several widely employed standard neurocognitive tests (1196). It is notable that a significant minority of participants opted to perform the hard option invariably for each trial, and this can be viewed from several angles. It could be said that these participants did not manifest any motivational impairment, as defined by this task. Alternatively, it could be argued that these participants responded in a somewhat suboptimal manner as they invested the same amount of effort for low-reward trials that had a low likelihood of payout as they did for high-value high-probability trials. Another possibility is that despite our efforts to calibrate the difficulty of the task to each individual, for some participants the task was still too easy and did not represent a significant challenge. These points aside, for two reasons, we recommend that future investigations employing this, or related paradigms, exclude or conduct a sensitivity analysis excluding participants who score at ceiling. First, it is not possible for participants with these scores to "improve;" this may be potentially be avoided by adding additional trials to the task or lengthening the trial duration in order to increase difficulty. Second, the test-retest consistency was more favourable and the magnitude of change over time was smaller when individuals scoring at ceiling were excluded.

The task took approximately 18 minutes to complete, and was on average not overly difficult or burdensome for participants. To this end, patients self-reported being driven to perform well on the task, highlighting the tolerability of this task in patients with schizophrenia. All participants, with the exception of one, were able to exceed the number of button presses required to complete a hard task during the post-task calibration run, suggesting that the task was not excessively exhausting. This lack of marked fatigue also underscores our findings of effort-related motivational impairment. That is, as patients were able to complete the number of button presses needed to complete the hard trial on request at the end of the task, we can infer that decisions to select the easy trial option during the task were related to participants' willingness to exert effort for the given reward, rather than an inability to actually complete the hard trial option.

Patients’ willingness to expend effort for reward was not related to severity of positive psychotic symptoms or neurocognition, highlighting the discriminant validity of the task. However, and contrary to expectations, we also did not find any significant association between task performance and motivational deficits or negative symptom severity. This may be related to our choice of clinical measures, which did not include a specific clinician-administered measure of
motivational deficits, and therefore represents a limitation of the current study. Rather, we included a self-report measure of motivational deficits; however, previous work has supported the validity of this approach (607). The lack of association between motivational deficit scores based on clinical rating scales and scores derived from a performance-based measure of effort-related motivation as observed in the present study is partly in line with some previous investigations (904, 1221, 1223, 1243); specifically, previous studies have reported inconsistent relationships with negative symptom severity, with some studies finding relationships using a categorical rather than continuous approach, while others have found a relationship collapsing diagnostic groups, and yet others reporting relationships with only specific aspects of task performance. In contrast to these findings are some studies reporting moderate overlap between clinical ratings of amotivation and effort performance (1222, 1255). Though we would expect some degree of convergence between these two assessment strategies, given the divergence in the methods employed to evaluate severity and the aspects of impairment captured, we would not expect the two to be redundant. Instead, we believe that the performance-based measure used in the present study provides a circumscribed evaluation of a specific aspect of motivation, whereas clinical ratings are broader and include several sources of variance, including the impact of situational factors.

We examined test-retest characteristics of this task in a convenience sample of patients with schizophrenia over a 2-week period. It remains to be seen if these characteristics would also be observed with a different retest timeframe, or if participants expected change as would be the case for participants enrolled in a clinical trial and receiving placebo. It is also unknown whether this task will remain valid among patients who are acutely ill or have severe motivational deficits. We did observe significant differences in effort performance among deficit versus nondeficit schizophrenia patients. Also, although we have demonstrated stability of performance on this task, it remains for future work to demonstrate sensitivity to treatment-related change. Notwithstanding these points, the present study advances the idea that motivational deficits can be assessed using an objective laboratory-based assessment tool in patients with schizophrenia. Specifically, we find that patients are able to comply with instructions, modify their choice behaviour in response to changing reward information, and are generally motivated to perform well. However, it seems that patients as a group reject the opportunity to work for valued rewards almost one-third of the time, even in a controlled laboratory setting. Furthermore, we
demonstrate task psychometric properties that are in line with other (cognitive) performance-based assessment tools already used in clinical trials (1196), suggesting that the present effort-based decision making paradigm may represent a novel paradigm that can be used to evaluate motivational impairments in patients with schizophrenia. As such, it may also prove useful in testing the efficacy of potential therapeutics aimed at ameliorating these impairments.
Chapter 9

9 Effect of Intrinsic Motivation on Cognitive Performance in Schizophrenia: A Pilot Study

Contents of this chapter have been published as: Fervaha G, Agid O, Foussias G, Remington G. Effect of intrinsic motivation on cognitive performance in schizophrenia: a pilot study. *Schizophrenia Research* 2014;152(1):317-318. (1216)


9.1 Introduction, Methods, Results, and Discussion

Poor effort is known to impact cognitive test performance (1025). In schizophrenia, a disorder associated with motivational deficits, poor mental effort has been found to predict a significant and sizeable portion of the variance in cognitive test performance (1131), a finding that has been replicated (1132). This suggests that cognitive impairment in schizophrenia may, at least in part, be explained by the presence of motivational deficits. However, the impact of motivation specifically related to cognitive testing procedures has not been explored in patients with schizophrenia, a domain that may be more closely related to test performance. The present study therefore set out to examine the impact of motivation to complete cognitive testing on cognitive test performance in patients with schizophrenia.

Twelve outpatients with a DSM-IV diagnosis of schizophrenia participated in the present study. Cognition was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB) (1196). Notably, the MCCB is the recommended assessment battery to be employed in clinical trials for cognition enhancing treatments for schizophrenia. Directly following administration of the MCCB, the Intrinsic Motivation Inventory (IMI) was administered (1031). The items of the IMI assess the amount that subjects are interested in, value, and had an autonomous choice to complete a task,
constructs grounded in self-determination theory (1031). In the present study, subjects were specifically instructed to complete the IMI based on the cognitive testing session. Also, to avoid potential response biases, the IMI was not labelled as a scale for the measurement of intrinsic motivation, rather it was labelled as an "activity scale." All analyses were carried out using IBM SPSS version 20. Statistical significance was set at $\alpha<0.05$ (two-tailed).

Demographic and clinical information of the study sample are reported in Table 9-1. Intrinsic motivation was significantly correlated with the cognitive composite score ($r = 0.59, p = 0.04$). This relationship held for all facets of intrinsic motivation (Interest: $r = 0.53, p = 0.08$; Value: $r = 0.48, p = 0.11$; Choice: $r = 0.51, p = 0.09$), albeit at statistical levels trending towards significance.

<table>
<thead>
<tr>
<th>Table 9-1. Demographic and clinical characteristics of study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schizophrenia (N=12)</strong></td>
</tr>
<tr>
<td><strong>Mean (S.D.) or N</strong></td>
</tr>
<tr>
<td><strong>Age, Years</strong></td>
</tr>
<tr>
<td>27.3 (5.0)</td>
</tr>
<tr>
<td><strong>Duration of Illness, Years</strong></td>
</tr>
<tr>
<td>5.6 (3.7)</td>
</tr>
<tr>
<td><strong>Gender (Male/Female)</strong></td>
</tr>
<tr>
<td>7/5</td>
</tr>
<tr>
<td><strong>Ethnicity, Number</strong></td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td><strong>African-Canadian</strong></td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td><strong>South-Asian</strong></td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td><strong>East-Asian</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td><strong>CPZ Equivalents</strong></td>
</tr>
<tr>
<td>546.0 (200.1)</td>
</tr>
</tbody>
</table>
The results of the present study demonstrate that level of intrinsic motivation specifically ascribed to cognitive test taking is significantly associated with cognitive test performance, suggesting that cognitive impairments in schizophrenia may partly be secondary to amotivation. While it is unlikely that the full extent and degree of cognitive impairment in schizophrenia results from motivational impairments (663), the amount of overlap is striking - intrinsic motivation levels explained approximately 35% of the variance in cognitive performance scores. One possible mechanistic explanation is that both motivational and cognitive deficits in schizophrenia result from impairments in the computation of effort cost (881). In the case of amotivation these are related to physical effort, and for cognition, mental effort costs. To this point, patients with schizophrenia have been found to expend less effort during cognitive tests than healthy control subjects (1271). This prediction entails that a common neural circuitry, likely relating to the reward network, underlies these two domains of psychopathology. There is some preliminary evidence for this. One study has demonstrated that activity within the ventral
striatum - a key node in the reward network - is associated with cognitive performance in healthy volunteers, but that this was not the case for patients with schizophrenia, thus suggesting a potential role for motivation deficits in cognitive performance (1272). Future studies evaluating cognitive performance in schizophrenia should assess for potential mediating variables, such as effort and motivation. This concern becomes particularly salient in clinical trials aimed at enhancing cognitive performance (1273). In such trials it should be elucidated whether changes in cognitive performance can be ascribed to "true" change in cognitive ability or to peripheral changes in level of motivation, effort, or other mediating variables.

In evaluating the present study, several limitations warrant mention. One such limitation was the small sample size included in this pilot study. Future studies should replicate and extend these findings in larger and more heterogeneous samples of patients. Furthermore, our study did not include patients with severe and unstable symptoms as well as those who were unwilling to participate. Future studies may wish to examine the relationship between motivation and cognitive performance in patients with prominent and/or persistent negative symptoms. Lastly, as the IMI was administered after completion of the cognitive testing, it may be possible that subjective experience during cognitive testing may have partly biased self-reports of intrinsic motivation. Notwithstanding these limitations, our results affirm a fundamental relationship between motivation and cognitive performance in schizophrenia. Greater attention to the assessment of motivational deficits, and their underlying neurobiology, may facilitate efforts aimed at ameliorating cognitive deficits and improving functional outcomes in patients with schizophrenia.
Chapter 10

10 Motivational Deficits and Cognitive Test Performance in Schizophrenia

Contents of this chapter have been published as: Fervaha G, Zakzanis KK, Foussias G, Graff-Guerrero A, Agid O, Remington G. Motivational deficits and cognitive test performance in schizophrenia. *JAMA Psychiatry* 2014;71(9):1058-1065. (878)


10.1 Introduction

Schizophrenia is a severe mental illness characterized by a constellation of signs and symptoms including positive (e.g., delusions), negative (e.g., lack of motivation) and cognitive (e.g., attention) symptoms (1274). Cognitive impairments and negative symptoms are considered core features of schizophrenia that also represent key predictors of functional outcomes (817, 821). Although these two domains of psychopathology are thought of as distinct and separable (663, 664), the influence of motivation, rather than broadly defined negative symptoms, on cognitive performance remains unclear (1275).

Cognitive ability is taken to be a stable feature of schizophrenia (1276), has been found to predict future development of the disorder in unaffected youth (193), and has been suggested to have the potential to serve as an endophenotype (1277). These notions rest on the assumption that performance on standard neuropsychological test measures is a valid proxy for cognitive ability. However, numerous factors can potentially influence test performance, such as internal drive to perform well. It therefore follows that cognitive test performance reflects both variance related to core cognitive processing ability as well as other external factors, such as the motivation to complete the testing procedures (Figure 10-1). Indeed, this parsing of cognitive test
performance into core cognitive information processing (i.e., computational processes) and motivational influence (i.e., energetic processes) has been described by many authors (1278-1283). Given the prominence of motivational deficits in schizophrenia, and the link between motivation and cognition, it is certainly reasonable to postulate that cognitive impairments seen in patients with the illness are, to some extent, secondary to motivational impairment.

![Diagram of the components of cognitive test performance]

**Figure 10-1. Illustration of the components of cognitive test performance**

The largest influence is hypothesized to be cognitive (i.e., information processing) ability. Level of intrinsic motivation and/or deployment of mental effort influences the link between ability and performance. Other factors (e.g., familiarity with tests, anxiety, etc.), may also impact performance, either through an influence on motivation or independently. It should also be noted that test performance can be interpreted as an observed variable, whereas the other factors such as cognitive ability are latent constructs.
While the notion of motivation and effort influencing performance has been established in healthy individuals and patients with neurological conditions (1025-1027, 1284), it is less well understood in schizophrenia. One study has demonstrated that a significant and sizeable portion of the variance in cognitive test performance can be explained by poor mental effort, as assessed by an instrument often used to detect suboptimal effort (1131), a finding that has been replicated (1132). Furthermore, two studies have shown that intrinsic motivation levels are significantly associated with cognitive performance (865, 866). The negative symptom of avolition (i.e., apathy) has also been shown to be associated with poorer cognitive performance (712, 850, 1024, 1285).

Our own pilot work suggests that motivation specifically ascribed to test taking accounts for a significant and sizeable portion of the variance in cognitive test scores in patients with schizophrenia (1216). There are, however, some conflicting findings. Specifically, one study reported a lack of association between cognitive test performance and intrinsic motivation levels related to approach or avoidance behaviour in patients with schizophrenia, as assessed by a personality questionnaire (1029); interestingly, this study did find a relationship between these measures in healthy volunteers. A subsequent study also failed to find a significant association between self-reported motivation and performance on working memory tests in patients using the same questionnaire (1286). Notwithstanding these inconsistent findings, motivation seems to impact cognitive test performance in patients with schizophrenia; however, this relationship needs to be confirmed (or disproved) in a sufficiently large sample of patients and tested across multiple domains of cognitive functioning. Given the surge of interest in cognition in schizophrenia, highlighted by the emergence of several recent clinical trials evaluating the effects of pharmacotherapy on cognitive performance (278), the role of potentially mediating or moderating variables such as motivation and effort on cognitive test performance in schizophrenia need to be better understood.

The present study set out to examine the relationship between intrinsic motivation and cognitive test performance in a large and heterogeneous sample of patients with schizophrenia. The association between motivation and global cognition, as well as individual domains of cognition, was evaluated. We hypothesized that level of intrinsic motivation would be significantly related to performance on cognitive tests; specifically, lower motivation would be associated with greater cognitive impairment both globally and for each individual cognitive domain. We further
hypothesized that the relationship between motivation and cognitive performance would be independent of clinical severity or functional status. In addition, longitudinal increases in motivation were hypothesized to be significantly related to improvements in cognitive performance.

10.2 Methods and Materials

10.2.1 Participants

Data were drawn from the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study for chronic schizophrenia. Details of the study design and rationale (1202), as well as primary findings (254), have been presented elsewhere. The primary purpose of the CATIE study was to compare the effectiveness of atypical and conventional antipsychotic medications through a randomized controlled trial conducted between January 2001 and December 2004 at 57 sites in the United States (16 university clinics, 10 state mental health agencies, 7 Veterans Affairs medical centers, 6 private nonprofit agencies, 4 private-practice sites, and 14 mixed-system sites). In the first phase of the trial, one thousand four hundred and ninety-three patients were randomized to receive olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions and were followed up to 18 months or until treatment was discontinued for any reason (1202). Patients had monthly visits with study doctors. The primary sample for the current study included individuals who were clinically stable, operationalized as no change in antipsychotic medication for the preceding 6 months. This inclusion criterion was implemented in order to increase generalizability of the current findings to other outcome studies as well as clinical trials focused on cognitive endpoints, both of which typically examine stable patients (1273).

The study inclusion criteria have been reported previously (1202). Briefly, participants were eligible if they were between the ages of 18 and 65 years and had a diagnosis of schizophrenia confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (1203). Participants were excluded from the study if they had a diagnosis of schizoaffective disorder, mental retardation, pervasive developmental disorder, delirium, dementia, amnesia or other
cognitive disorders; if they had only one episode of schizophrenia; were pregnant or breast-feeding; or had a serious and acutely unstable medical condition.

The study was approved by the institutional ethics review board at each site, and written informed consent was obtained from the patients or their legal guardians. All participants demonstrated adequate decision-making capacity in regards to participating in the study as determined by the MacArthur Competence Assessment Tool (1228).

10.2.2 Instruments and Procedure

The neuropsychological tests that comprised the CATIE cognitive battery have been described in detail in a previous report (1214). Scores on individual tests were converted to z-scores and combined to construct the following cognitive domain scores: 1) processing speed, calculated as the average of the Revised Wechsler Adult Intelligence Scale Digit Symbol Test, Grooved Pegboard, and the mean of the Controlled Oral Word Association Test and category instances; 2) working memory, as measured by the average of the Letter-Number sequencing test and a computerized test of visuospatial working memory; 3) verbal memory, assessed with the average of three trials from the Hopkins Verbal Learning Test; 4) vigilance, as evaluated by the d-prime summary score from the Continuous Performance Test; and 5) reasoning, measured by an average score from the Revised Wechsler Intelligence Scale for Children Mazes test and a computerized version of the Wisconsin Card Sorting Test (661). Of note, these are all domains assessed by the MATRICS cognitive consensus battery (1196, 1287). The 5 domain scores were then averaged to create a cognitive composite score. Details on the baseline characteristics of neurocognition (661) and response to treatment (1219) in the CATIE study have been published previously.

Intrinsic motivation was evaluated using the sum of three items from intrapsychic foundations subscale of the Heinrichs-Carpenter Quality of Life Scale (QLS) (1197): sense of purpose, motivation and curiosity. These items measure general trait-like motivation, and tap into core constructs within self-determination theory, which defines intrinsic motivation as the interest in, drive towards, and enjoyment of activities and goals for their own sake (i.e., even in the absence of specific extrinsic rewards) (940). While there is no "gold standard" instrument for the
assessment of intrinsic motivation in schizophrenia, this derived 3-item measure has been utilized in numerous empirical studies examining this construct in patients with schizophrenia (765, 865, 866, 871, 879, 880, 1210, 1211). The measure demonstrated good internal consistency in the present sample (Cronbach's $\alpha = 0.80$). The QLS is a clinician-administered instrument that evaluates various functional domains over the past 4 weeks.

Other measures of interest included the Clinical Global Impression – Severity scale (CGI-S) to assess overall clinical severity (556), Positive and Negative Syndrome Scale (PANSS) to assess psychopathology (474), Calgary Depression Scale for Schizophrenia (CDSS) to assess depressive symptoms (649), and the QLS, excluding the intrapsychic foundations domain, to assess psychosocial and community functioning (1197).

10.2.3 Statistical Analyses

Bivariate relationships were examined using Pearson's product-moment correlation coefficients. To test the robustness of these correlations 95% bias corrected accelerated confidence intervals (CIs) were estimated using 10,000 bootstrap samples, drawn by randomly re-sampling with replacement from the original dataset (1288). Next partial correlations were conducted to examine the relationship between intrinsic motivation scores and cognitive test performance, while statistically controlling for other clinical variables (e.g., CGI-S). Potential differences in magnitude of association between the variables were calculated using Steiger’s test for dependant correlation coefficients (1289, 1290). The relationship between change in level of intrinsic motivation and change in cognitive test performance was also examined through a partial correlation analysis, controlling for baseline scores in the primary sample of stable patients. Analyses were conducted on stable patients with schizophrenia who served as the primary sample in the present study; however, we also confirmed these relationships in the full CATIE sample in order to examine generalizability of findings to a larger and more heterogeneous sample of patients, as well as in a sub-sample of patients who were antipsychotic-free at baseline. Statistical tests were considered significant at a p-value of less than 0.05 (two-tailed). All analyses were conducted in SPSS Statistics version 20 (IMB Corp., Armonk, NY, USA).
10.3 Results

10.3.1 Patient Characteristics

Cognitive, symptom and functioning data were available for 431 patients with schizophrenia who remained on the same medication for 6 months. Sociodemographic and clinical characteristics of the sample are presented in Table 10-1. Notably, the mean level of intrinsic motivation for the present sample was comparable with that reported in other schizophrenia samples (765, 865, 866, 871, 879, 880), which reflects moderate deficits in intrinsic motivation.

Table 10-1. Sociodemographic and clinical characteristics of sample (N = 431)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (S.D.) or %</th>
<th>Range (min - max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.7 (11.0)</td>
<td>18 - 66</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>75.9</td>
<td>-</td>
</tr>
<tr>
<td>Race (% White)</td>
<td>62.6</td>
<td>-</td>
</tr>
<tr>
<td>Patient’s Education (years)</td>
<td>12.1 (2.2)</td>
<td>3 - 21</td>
</tr>
<tr>
<td>Antipsychotic Duration (years)</td>
<td>14.6 (11.4)</td>
<td>0 - 56</td>
</tr>
<tr>
<td>Employment (% unemployed)</td>
<td>82.8</td>
<td>-</td>
</tr>
<tr>
<td>CGI-S</td>
<td>3.9 (1.0)</td>
<td>1 - 7</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>63.3 (15.9)</td>
<td>30 - 109</td>
</tr>
<tr>
<td>PANSS - Positive</td>
<td>14.2 (4.9)</td>
<td>7 - 30</td>
</tr>
<tr>
<td>PANSS - Negative</td>
<td>17.8 (5.8)</td>
<td>7 - 34</td>
</tr>
</tbody>
</table>
10.3.2 Association between Motivation and Cognition in Stable Patients

Level of intrinsic motivation was significantly and positively correlated with the cognitive composite score, as well as scores from each individual domain of cognition (Figure 10-2; Figure 10-3). Further, each individual item within the intrinsic motivation measure was significantly and positively correlated with the cognitive composite score, as well as scores from each individual domain of cognition (Table 10-4). Level of motivation was more strongly associated with processing speed performance than scores on tests of reasoning ($z = 3.25$, $p = 0.001$), vigilance ($z = 2.95$, $p = 0.003$), and working memory ($z = 2.41$, $p = 0.02$); the magnitude of association between motivation and other cognitive domains did not differ (all $p$’s $> 0.05$). Intrinsic motivation was found to be associated with cognitive test performance for individuals on each antipsychotic medication, even after controlling for dose (Table 10-5).
Figure 10-2. Graphical depiction of the strength of the bivariate relationship between intrinsic motivation level and each cognitive domain score for 431 patients with schizophrenia

Level of motivation was correlated with the cognitive composite score ($r = 0.33$, $p < 0.001$; 95% bias corrected confidence interval [CI]: 0.25 – 0.40), verbal memory ($r = 0.27$, $p < 0.001$; CI: 0.18 – 0.34), vigilance ($r = 0.22$, $p < 0.001$; CI: 0.13 – 0.31), processing speed ($r = 0.34$, $p < 0.001$; CI: 0.26 – 0.42), reasoning ($r = 0.20$, $p < 0.001$; CI: 0.11 – 0.29), and working memory ($r = 0.25$, $p < 0.001$; CI: 0.17 – 0.33).

The relationship between intrinsic motivation and cognitive test performance remained after individually controlling for severity of illness as indexed by the CGI-S ($r = 0.29$, $p < 0.001$), PANSS total score ($r = 0.28$, $p < 0.001$), PANSS positive subscale ($r = 0.31$, $p < 0.001$), PANSS negative subscale ($r = 0.26$, $p < 0.001$), PANSS general psychopathology subscale ($r = 0.30$, $p < 0.001$), or the CDSS ($r = 0.34$, $p < 0.001$). The association between motivation and cognitive performance also remained significant when controlling for other clinical variables such as years of antipsychotic treatment ($r = 0.28$, $p < 0.001$), or presence of medical co-morbidity ($r = 0.31$, $p < 0.001$). This relationship also held when the variance attributed to all indices of illness severity was partialed out together ($r = 0.20$, $p < 0.001$), suggesting that this relationship is not secondary to symptom severity.
Motivation continued to demonstrate a significant relationship with cognitive test performance when sociodemographic variables were statistically accounted for such as age ($r = 0.30, p < 0.001$), sex ($r = 0.33, p < 0.001$), race ($r = 0.32, p < 0.001$), or years of education ($r = 0.27, p < 0.001$). The relationship also held when all these sociodemographic variables were controlled concurrently ($r = 0.23, p < 0.001$).

Previous work has suggested that two constructs may be related not because they are inherently linked, but rather because of a shared relationship with distal outcome variables(663). As both motivation and cognition were related to functional status ($r = 0.57, p < 0.001$; $r = 0.22, p < 0.001$; respectively), we re-examined the association between these variables after statistically accounting for functioning scores. The relationship between level of intrinsic motivation and cognition remained even after controlling for community functioning ($r = 0.25, p < 0.001$). It is also worth mentioning that the relationship between motivation and performance on tests from individual cognitive domains also remained significant while controlling for sociodemographic, clinical and functioning variables (Table 10-6).

Lastly, prospective increases in motivation were found to be significantly related to improvements in cognitive performance (Table 10-2). This relationship between longitudinal change in motivation and change in cognitive test performance remained after accounting for the change in clinical variables, albeit at a level trending towards significance (Table 10-7); however, controlling for change in functional status nullified this association.

**Table 10-2. Impact of longitudinal change in intrinsic motivation on change in cognitive test performance**

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Correlation with change in intrinsic motivation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite score</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>0.10</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Next, we wanted to explore whether this relationship would be observed in the entire CATIE sample by examining baseline data (N = 1322). Even in this large and heterogeneous group of patients, intrinsic motivation had a significant association with cognitive test performance (Table 10-3). This relationship held for a subsample of 351 antipsychotic-free patients who reported not receiving any antipsychotic medication for at least the preceding two weeks (r = 0.31, p < 0.001).

### Table 10-3. Bivariate correlations between level of intrinsic motivation and cognitive scores for all CATIE participants with available data (N = 1322)

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Intrinsic Motivation</th>
<th>95% CI (lower, upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite score</td>
<td>0.33</td>
<td>(0.29, 0.38)</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>0.29</td>
<td>(0.24, 0.33)</td>
</tr>
<tr>
<td>Vigilance</td>
<td>0.21</td>
<td>(0.16, 0.27)</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.32</td>
<td>(0.27, 0.37)</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.20</td>
<td>(0.15, 0.25)</td>
</tr>
</tbody>
</table>
**10.4 Discussion**

The present study examined the association between intrinsic motivation and cognitive performance in individuals with schizophrenia. Our results reveal that poor motivation is significantly associated with worse performance on tests of processing speed, working memory, verbal memory, vigilance and reasoning, suggesting that cognitive impairments in schizophrenia may partly be secondary to amotivation. Importantly, this association between motivation and performance cannot be explained by severity of psychopathology or by shared variance with functioning scores.

We wish to emphasize that that the present results do not suggest that the full extent and degree of cognitive impairment in schizophrenia result from motivational impairments; previous work has, in fact, shown cognitive deficits even in patients who invest adequate effort (1131). Nonetheless, an association in the moderate effect size range was elucidated. Intrinsic motivation levels predicted between 6 and 16% of the variance in global cognitive performance scores.

One possible mechanistic explanation for the link between motivation and cognitive performance is that both amotivation and cognitive deficits in schizophrenia result at least partially from impairments in the computation of effort demands (881). In the case of apathy, these are related to physical effort, while for cognition it is mental effort costs. Cognitive functioning has been
shown to carry inherent action costs (1109), and patients with schizophrenia have been found to invest less effort during cognitive tests than healthy individuals (1271). In addition, deficits in patients' willingness to expend physical effort have been found to be related to their performance on cognitive tests (904, 1221); though, one study did not find such a relationship using a different measure of effort-related motivation (1255). Having both motivation and cognitive deficits linked to aberrant effort computations suggests that both of these domains are associated with a common neural architecture, likely related to dopamine signalling and fronto-striatal circuit functioning (881). There is, in fact, some evidence supporting this; for example, one study has shown that activity within the ventral striatum is associated with cognitive performance in healthy volunteers although this is not the case for patients with schizophrenia (1272). Whether compromised cognitive performance is due to motivational deficits, increased task difficulty, or an interaction between these is generally difficult to disentangle however, and studies wishing to assess one construct independent of the other will need to carefully select tasks. Nevertheless, future studies evaluating cognition in schizophrenia should examine potential mediating/moderating variables such as effort and motivation. This concern becomes particularly important in clinical trials evaluating interventions that putatively enhance cognition (1273). In such trials it should be elucidated whether changes in cognitive performance can be ascribed to change in core cognitive functioning or, instead, to peripheral changes in level of motivation/effort (Figure 10-1). We also recommend that individuals who demonstrate poor motivation should be identified in such trials, and that subanalyses be conducted excluding individuals identified as putting forth suboptimal effort. Although there is no "gold standard" for how to detect such cases among individuals with schizophrenia, perhaps a stringent threshold on one or more performance validity test could suffice for this purpose. Future studies should empirically establish an instrument to assess motivation specifically in the context of cognitive testing with schizophrenia patients.

Our results have important implications regarding our understanding of cognitive deficits in schizophrenia. First, they suggest that cognitive performance should change by simply enhancing the intrinsic value of the testing procedures. There is some preliminary evidence of this, in that offering task instructions in a "game-like" fashion, thus increasing the intrinsic value of the task, has been found to increase learning in patients with schizophrenia (1291). At the same time, variables that undermine motivation such as defeatist beliefs, which may decrease the intrinsic
value ascribed to a task, have been found to be associated with lower cognitive performance (815). These findings, of course, also have implications for cognitive training or remediation programs (1292). Second, although not directly related to intrinsic motivation, these results leave open the possibility that increasing motivation more broadly defined (which includes extrinsic motivation (1293)) will increase performance. There are several older studies that have confirmed this assertion (1294-1297). Similarly, interventions that affect motivation and effort should also impact cognitive performance. To this point, it has been shown that increasing dopaminergic transmission via amphetamine which is well known to affect motivation and reward processing, improves performance on cognitive tests (1267, 1268, 1298). Taken together, level of motivation clearly has an association with cognitive test performance in schizophrenia.

In evaluating the present study, limitations should be mentioned. First, the measure employed to assess intrinsic motivation was derived from the QLS rather than being a standalone measure. Recently, an intrinsic motivation inventory has been developed for, and validated with, schizophrenia patients (1031); we have used this specific measure in a previous study and the results are consistent with those presented here (1216). Second, our assessment of intrinsic motivation relied on a single measure. Though this measure included three distinct items and each demonstrated a relationship with cognitive performance, future studies should examine whether multiple indicators of motivation and effort (e.g., performance validity tests) might explain a greater portion of variance in cognitive test performance. Third, the relationship between change in intrinsic motivation and change in cognitive test performance, though statistically significant, was of a modest effect size. This may partly be due to the relatively small improvement in cognition scores (1219), and level of intrinsic motivation (estimated mean difference = 0.53; paired sample t-test, t = 2.65, df = 428, p = 0.008) seen following antipsychotic treatment; a more robust relationship might be observed following more substantive changes in both cognitive performance and motivation. Fourth, although the present results are interpreted as intrinsic motivation impacting cognitive performance scores, directionality cannot be established with the present set of analyses. It remains possible that cognitive impairment undermines volition. Finally, the influence of motivation and effort on cognitive test performance is not specific to individuals with schizophrenia (1025-1027); however, the prevalence of motivational deficits in this disorder suggests that this relationship may be particularly salient and ought to be taken into account.
Moving forward, the present results strongly encourage the assessment of variables such as motivation and effort when evaluating cognitive performance in schizophrenia. Taking these other variables into account may enhance the discovery of variables (e.g., genetic) that are specifically related to core neurocognitive ability. At the very least, our results suggest that poor cognitive test performance scores should not be inferred at face value to purely reflect impairment in neural processes subserving the cognitive process in question (i.e., neuroanatomical localization). In addition, our findings suggest that in the ongoing search for therapeutics to improve functional outcomes among individuals with schizophrenia a greater focus on motivational and effort-based deficits, as well as their underlying neurobiology, or indeed the shared mechanisms underlying the motivation-cognition relationship, may facilitate efforts aimed at ameliorating these impairments and improving outcomes.

10.5 Additional Tables and Figures

Table 10-4. Bivariate correlations between intrinsic motivation items and cognitive test scores

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Sense of purpose</th>
<th>Motivation</th>
<th>Curiosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite score</td>
<td>0.27***</td>
<td>0.21***</td>
<td>0.26***</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>0.24***</td>
<td>0.21***</td>
<td>0.23***</td>
</tr>
<tr>
<td>Vigilance</td>
<td>0.21***</td>
<td>0.16**</td>
<td>0.19***</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.29***</td>
<td>0.24***</td>
<td>0.25***</td>
</tr>
<tr>
<td>Reasoning</td>
<td>0.18***</td>
<td>0.10*</td>
<td>0.18***</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.16***</td>
<td>0.11*</td>
<td>0.18***</td>
</tr>
</tbody>
</table>
Correlations are significant at the *p<0.05; **p<0.01; or ***p<0.001 level.

Table 10-5. Bivariate correlations between level of intrinsic motivation and global cognitive test performance stratified by medications

<table>
<thead>
<tr>
<th>Antipsychotic medication</th>
<th>Correlation with intrinsic motivation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Partial correlation with intrinsic motivation controlling for dose&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine (N = 129)</td>
<td>0.39***</td>
<td>0.38***</td>
</tr>
<tr>
<td>Perphenazine (N = 70)</td>
<td>0.35**</td>
<td>0.35**</td>
</tr>
<tr>
<td>Quetiapine (N = 80)</td>
<td>0.34**</td>
<td>0.34**</td>
</tr>
<tr>
<td>Risperidone (N = 105)</td>
<td>0.21*</td>
<td>0.21*</td>
</tr>
<tr>
<td>Ziprasidone (N = 47)</td>
<td>0.31*</td>
<td>0.30*</td>
</tr>
</tbody>
</table>

Correlations were statistically significant at the *p<0.05; **p<0.01; or ***p<0.001 level.

<sup>a</sup>Bivariate correlation with cognitive composite score.

<sup>b</sup>Dose range for medications were as follows: olanzapine (7.5-30 mg/day), perphenazine (8-32 mg/day), quetiapine (200-800 mg/day), risperidone (1.5-6 mg/day), and ziprasidone (40-160 mg/day).

Table 10-6. Partial correlations between level of intrinsic motivation and specific domain cognitive performance scores controlling for other variables

<table>
<thead>
<tr>
<th>Variable being statistically correlated</th>
<th>Partial correlation</th>
<th>Partial correlation</th>
<th>Partial correlation</th>
<th>Partial correlation</th>
<th>Partial correlation</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>controlled for</th>
<th>between motivation and verbal memory</th>
<th>between motivation and vigilance</th>
<th>between motivation and processing speed</th>
<th>between motivation and reasoning</th>
<th>between motivation and working memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-S</td>
<td>0.23***</td>
<td>0.20***</td>
<td>0.32***</td>
<td>0.16***</td>
<td>0.21***</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>0.23***</td>
<td>0.20***</td>
<td>0.31***</td>
<td>0.17***</td>
<td>0.21***</td>
</tr>
<tr>
<td>PANSS – Positive</td>
<td>0.27***</td>
<td>0.22***</td>
<td>0.34***</td>
<td>0.19***</td>
<td>0.23***</td>
</tr>
<tr>
<td>PANSS – Negative</td>
<td>0.20***</td>
<td>0.17***</td>
<td>0.28***</td>
<td>0.15***</td>
<td>0.20***</td>
</tr>
<tr>
<td>PANSS – General</td>
<td>0.25***</td>
<td>0.21***</td>
<td>0.33***</td>
<td>0.18***</td>
<td>0.23***</td>
</tr>
<tr>
<td>Depression (CDSS)</td>
<td>0.28***</td>
<td>0.24***</td>
<td>0.36***</td>
<td>0.20***</td>
<td>0.27***</td>
</tr>
<tr>
<td>Functioning (QLS)</td>
<td>0.15***</td>
<td>0.16**</td>
<td>0.25***</td>
<td>0.17***</td>
<td>0.23***</td>
</tr>
<tr>
<td>Years of antipsychotic treatment</td>
<td>0.24***</td>
<td>0.21***</td>
<td>0.31***</td>
<td>0.14**</td>
<td>0.21***</td>
</tr>
<tr>
<td>Medical co-morbidity</td>
<td>0.26***</td>
<td>0.21***</td>
<td>0.33***</td>
<td>0.19***</td>
<td>0.24***</td>
</tr>
<tr>
<td>Age</td>
<td>0.25***</td>
<td>0.21***</td>
<td>0.32***</td>
<td>0.16***</td>
<td>0.23***</td>
</tr>
<tr>
<td>Sex</td>
<td>0.25***</td>
<td>0.22***</td>
<td>0.34***</td>
<td>0.23***</td>
<td>0.25***</td>
</tr>
<tr>
<td>Variable being statistically controlled for</td>
<td>Correlation between change in intrinsic motivation and change in global cognitive performance</td>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in CGI-S</td>
<td>0.09</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in PANSS Total</td>
<td>0.09</td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in PANSS – Positive</td>
<td>0.10</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in PANSS – Negative</td>
<td>0.10</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in PANSS – General</td>
<td>0.09</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in depression (CDSS)</td>
<td>0.10</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in functioning (QLS)</td>
<td>0.06</td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CGI-S: Clinical Global Impression - Severity; PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia; QLS: Heinrichs-Carpenter Quality of Life Scale excluding the intrapsychic foundations subscale.

Correlations were statistically significant at the *p<0.05; **p<0.01; or ***p<0.001 level.

Table 10-7. Partial correlations between change in intrinsic motivation and change in cognitive composite score controlling for other variables
Abbreviations: CGI-S: Clinical Global Impression - Severity; PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia; QLS: Heinrichs-Carpenter Quality of Life Scale excluding the intrapsychic foundations subscale.

Figure 10-3. Scatterplot showing level of intrinsic motivation and cognitive test performance (composite cognitive performance scores)
11 Antipsychotics and Amotivation

11.1 Introduction

Negative symptoms are a prevalent and prominent feature of schizophrenia (822). These include many broad signs and symptoms including blunted affect, alogia, and avolition/amotivation. Amotivation refers specifically to the inability to initiate and sustain goal-directed activity relating to a diminished sense of drive. The use of this term herein does not connote a complete absence of motivation, but rather we imply a degree of motivational deficit. What would later be defined as negative symptoms were described decades before the introduction of antipsychotic medications (14, 23), clearly establishing primary negative symptoms as distinguishable from secondary medication effects. Further to this point, negative symptoms are evident in first-episode, antipsychotic-naïve individuals (484), as well as individuals in the putative prodrome before the onset of frank psychosis (1165).

Antipsychotic drugs have been identified as a causative factor in secondary (i.e., iatrogenic) negative symptoms, which may also aggravate primary (i.e., idiopathic) negative symptoms related to the underlying illness (487, 488, 519). In terms of mechanism of action, antipsychotics block dopamine (D2) receptors (242), and it is this reduction in dopaminergic transmission that has been linked to the dampened ability of organisms to attribute incentive salience and drive in a multitude of pre-clinical studies (493). While there is evidence that a single administration of an antipsychotic leads to some degree of motivation impairment (496-498), although not
consistently (499), evidence linking chronic treatment to these deficits does not exist. Higher dopamine D2 receptor blockade has been linked to worse subjective experiences (i.e., greater dysphoria) in patients chronically treated with antipsychotics (511, 1158), but subjective experience and dysphoria do not speak to motivation deficits per se. Seemingly paradoxically, negative symptoms have also been found to improve following antipsychotic treatment (270, 500), even in non-psychotic individuals (501), and withdrawal of antipsychotic medication has been linked to worsening of negative symptom burden in patients with schizophrenia (502-505).

Several studies have examined whether higher doses of antipsychotics are related to more severe negative symptoms (broadly defined) and have failed to confirm such an association (484, 506, 507); moreover, average dose of antipsychotic received during acute exacerbation is not related to degree of change in negative symptoms (484). Other studies have failed to link higher antipsychotic occupancy of the dopamine D2 receptor with more severe negative symptoms, or with reduction in these symptoms (511). More recent clinical studies examining patients chronically treated with antipsychotics have reported that patients receiving higher dosages of antipsychotic medication are not more impaired in their willingness to expend effort in pursuit of goals (904, 1221, 1222, 1255); moreover, at least a subpopulation of chronically treated patients do not differ from untreated healthy controls (904, 1222). In line with this, one pre-clinical investigation has demonstrated that goal pursuit following chronic haloperidol treatment is no different than following vehicle treatment (1299). These findings taken together suggest that chronic treatment with antipsychotic medication may not necessarily worsen the amotivational state associated with schizophrenia.

In the present study we examine the effect of antipsychotics on motivational deficits in particular, rather than negative symptoms more broadly, as these symptoms have emerged as a discrete aspect of negative symptoms as supported by a host of factor analytic studies (666), are differentially related to outcome variables (673), and may therefore have different underlying mechanisms than other negative symptoms such as reduced emotional expression. Specifically, the present study examines whether motivational deficits were related to antipsychotics in a dose-dependent fashion using a large sample of individuals maintained on selected antipsychotics. We further examined whether motivational deficits would worsen in antipsychotic-free individuals subsequently started on, and chronically treated with, a single
antipsychotic medication. Based on the available clinical evidence, we hypothesized that antipsychotic dose would not be related to degree of amotivation.

11.2 Materials and Methods

11.2.1 Study Design

Data were collected as part of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) schizophrenia study; for which the details of the study design and primary results are reported elsewhere (254, 1202). The CATIE project conducted between January 2001 and December 2004 at 57 sites in the United States was designed to examine the effectiveness of atypical and a single typical antipsychotic medication for the treatment of chronic schizophrenia.

Participants were eligible to participate in the CATIE study if they were between the ages of 18 and 65 years and had a diagnosis of schizophrenia confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (1203). Participants were excluded from the study if they had a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; had a documented history of treatment refractory illness; or had a serious and unstable medical condition. Eligible participants were initially randomized to olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), risperidone (1.5 to 6.0 mg per day), or ziprasidone (40 to 160 mg per day) under double-blind conditions and were followed for up to 18 months or until treatment was discontinued for any reason (1202). Patients could receive between one and four capsules of study medication, corresponding to the minimum and maximum amounts noted above.

The study was approved by the institutional ethics review board at each site, and written informed consent was obtained from the patients or their legal guardians. All participants demonstrated adequate decision-making capacity in regard to participating in the CATIE study as determined by the MacArthur Competence Assessment Tool (1228).
11.2.2 Participants

Individuals who received the same antipsychotic medication for at least 6 months were included in the present analysis. Only individuals judged to have been actually receiving the medication were included in the present analysis (i.e., rated as taking their medication 'always' or between 75-100% of the time). Medication adherence was evaluated on a single global item based on all available information including pill count and information from patients (1202).

In addition, participants who reported not receiving any antipsychotic medication for at least the preceding two weeks were included in a separate analysis examining longitudinal change in level of motivation following 6 months of antipsychotic treatment. Notably, these participants were not medication-naive, but had received antipsychotic treatment in the past.

11.2.3 Measures

Motivation was evaluated using 3 items from the intrapsychic foundations subscale of the Heinrichs-Carpenter Quality of Life Scale (QLS) (1197): curiosity, goal-directed motivation and sense of purpose (865). The QLS is a rater-administered semi-structured interview instrument, and this derived measure of motivation is thought to index general motivation (i.e., the ability or willingness to engage in goal-directed activities, not linked to any specific task or incentive scheme), and deficits therein. Though there is no gold standard instrument for the assessment of motivation in people with schizophrenia, this measure has been used in numerous empirical studies (765, 865, 866, 871, 879, 1210, 1211). We evaluated the reliability of this motivation measure in a subsample of individuals in the present study who did not evince a prospective change in antipsychotic dosage over 6 months. This measure demonstrated high longitudinal consistency (intraclass coefficient = 0.82). Importantly, this measure has been found to be sensitive to change over time (765, 871). In terms of construct validity, this measure has been shown to have significant overlap with other measures of amotivation (1211), but conversely has not been linked with severity of positive symptoms (1210), or depressive symptoms (765). These latter findings of discriminant validity are echoed here; motivation was only weakly associated with severity of positive symptoms ($r = -0.24, P < 0.001$) and depression as measured with the Calgary Depression Scale for Schizophrenia ($r = -0.17, P < 0.001$)(650). In the present sample, a
higher level of motivation was significantly associated with lower negative symptom burden ($r = -0.46$, $P < 0.001$); however, this translates to approximately 21% overlap between the two measures, suggesting that the motivation measure is not redundant with more broad negative symptom assessment and therefore may be evaluating a somewhat distinct construct. Higher scores on this measure reflect a greater level of motivation.

The Positive and Negative Syndrome Scale (PANSS) was used to evaluate severity of psychopathology (474). The PANSS is a clinician-rated instrument that includes 30 items: 7 evaluating positive symptoms (e.g., hallucinations), 7 evaluating negative symptoms (e.g., blunted affect), and 16 assessing general psychopathology (e.g., anxiety). Higher scores on this scale reflect greater symptom severity.

A secondary measure of amotivation was also employed. Specifically, a social amotivation score was derived by summing the following items from the PANSS: emotional withdrawal, passive apathetic withdrawal, and active social avoidance (685). These items have been shown to form a separate subfactor within the PANSS negative symptoms factor (683, 685), and represent items that demonstrate the highest convergence with more detailed amotivation measures (693). This measure was moderately related to the motivation measure derived from the QLS ($r = -0.44$, $P < 0.001$). Notably, the QLS motivation measure demonstrated a significantly higher degree of overlap with the social amotivation score, compared with a diminished expression score also derived from the PANSS ($r = -0.36$, $P < 0.001$; Steiger's test: $z = 2.19$, $P = 0.01$) (685). This PANSS derived social amotivation score also demonstrated good test-retest reliability (intraclass coefficient = 0.78). Higher scores on this social amotivation measure reflect greater motivational deficits.

Extrapyramidal symptoms were evaluated using an abbreviated version of the Simpson-Angus Scale (1195, 1213). This instrument includes 6 items which are rated based on clinical examination, where higher scores denoting more severe extrapyramidal side effects. The specific items include: gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, and tremor.

Sedation (i.e., sleepiness) and akinesia were evaluated using a single item which was rated on a 0 to 3 scale, where higher scores reflected greater severity. For these items, clinicians were instructed to not rate symptoms related to schizophrenia that, for example, are included in the PANSS.
11.2.4 Statistical Analyses

The effect of antipsychotic dose on motivation scores was examined using analysis of covariance models, adjusting for age, sex and severity of positive symptoms. Separate models were constructed for each antipsychotic medication. Notably, although we include severity of positive symptoms as a covariate as an index of general clinical severity, the results remain unchanged if instead of this variable, severity of negative symptoms, or severity of overall symptoms are included in the models.

Collapsing across drugs and doses, another model was constructed to examine whether individuals differed on their level of motivation based on the medication they were receiving, and further whether there was differential change in motivation as a function of specific antipsychotic received. This latter analysis was conducted using a repeated-measures analysis of covariance model, adjusting for age, sex, and changes in positive symptoms.

Longitudinal change in level of motivation was also examined in individuals who were antipsychotic-free at baseline. This was done by computing a repeated-measures analysis of variance model which did not include any covariates.

The relationships between level of amotivation and severity of side effects such as sedation and akinesia were quantified using Spearman rank-order correlation coefficients. Statistical significance was set at $P < 0.05$ (two-tailed) and analyses were carried out using SPSS version 20 (IBM Corporation, Armonk, NY).

11.3 Results

11.3.1 Participant Characteristics

Sociodemographic and clinical characteristics of the study sample are presented in Table 11-1. Five hundred and twenty individuals who received that same antipsychotic medication for 6 months and had available data on motivation were included in the present study.
Table 11-1. Demographic and clinical characteristics for study sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (S.D.) or %</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.0 (11.3)</td>
<td>18 - 66</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>74.6</td>
<td>-</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>63.0</td>
<td>-</td>
</tr>
<tr>
<td>Black</td>
<td>32.6</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>4.4</td>
<td>-</td>
</tr>
<tr>
<td>Employment status (unemployed)</td>
<td>83.7</td>
<td>-</td>
</tr>
<tr>
<td>Patient’s education (years)</td>
<td>12.1 (2.3)</td>
<td>3 - 21</td>
</tr>
<tr>
<td>Illness duration (years since first prescribed antipsychotic medication)</td>
<td>15.1 (11.5)</td>
<td>0 - 56</td>
</tr>
<tr>
<td>Motivation score</td>
<td>7.9 (4.2)</td>
<td>0 - 18</td>
</tr>
<tr>
<td>Social amotivation score</td>
<td>9.2 (3.4)</td>
<td>3 - 18</td>
</tr>
<tr>
<td>Symptoms at 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (total score)</td>
<td>64.4 (16.6)</td>
<td>30 - 122</td>
</tr>
<tr>
<td>PANSS – positive subscale score</td>
<td>14.6 (5.0)</td>
<td>7 - 35</td>
</tr>
<tr>
<td>PANSS – negative subscale score</td>
<td>17.9 (5.9)</td>
<td>7 - 37</td>
</tr>
<tr>
<td>PANSS – general psychopathology subscale score</td>
<td>31.9 (8.7)</td>
<td>16 - 63</td>
</tr>
<tr>
<td>Motivation score</td>
<td>8.6 (4.2)</td>
<td>0 - 18</td>
</tr>
</tbody>
</table>
Social amotivation score 8.3 (3.2) 3 - 18

Abbreviations: PANSS: Positive and Negative Syndrome Scale.

### 11.3.2 Medication Type and Amotivation

The severity of motivational impairment for individuals receiving each medication for 6 months is reported in Table 11-2. No main effect of antipsychotic medication type on level of motivation was observed ($F_{1,506} = 0.62, \ p = 0.43$). Furthermore, there was no indication that level of motivation differentially changed based on the specific antipsychotic medication received (drug-by-time interaction; $F_{1,506} = 0.46, \ p = 0.69$), suggesting that specific antipsychotic drugs do not undermine, or promote, motivation to a differential degree.

<table>
<thead>
<tr>
<th>Antipsychotic medication</th>
<th>Motivation at 6-months</th>
<th>Social amotivation at 6-months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
</tr>
<tr>
<td>Olanzapine (N=155)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.3 (4.0)</td>
<td>8.2 (3.3)</td>
</tr>
<tr>
<td>Dose 1 (7.5 mg; N=16)</td>
<td>9.8 (5.5)</td>
<td>7.0 (3.1)</td>
</tr>
<tr>
<td>Dose 2 (15 mg; N=49)</td>
<td>9.1 (3.6)</td>
<td>8.2 (3.5)</td>
</tr>
<tr>
<td>Dose 3 (22.5 mg; N=45)</td>
<td>7.2 (4.0)</td>
<td>7.9 (3.3)</td>
</tr>
<tr>
<td>Dose 4 (30 mg; N=44)</td>
<td>7.8 (3.7)</td>
<td>8.8 (3.0)</td>
</tr>
<tr>
<td>Perphenazine (N=88)</td>
<td>8.5 (4.4)</td>
<td>8.0 (3.5)</td>
</tr>
<tr>
<td>Dose 1 (8 mg; N=9)</td>
<td>8.4 (3.6)</td>
<td>6.9 (2.7)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Dose 2 (16 mg; N=29)</td>
<td>9.9 (4.1)</td>
<td>7.6 (3.2)</td>
</tr>
<tr>
<td>Dose 3 (24 mg; N=22)</td>
<td>7.7 (4.2)</td>
<td>8.9 (4.3)</td>
</tr>
<tr>
<td>Dose 4 (32 mg; N=28)</td>
<td>7.8 (5.0)</td>
<td>8.0 (3.3)</td>
</tr>
<tr>
<td>Quetiapine (N=100)</td>
<td>9.0 (4.3)</td>
<td>8.1 (2.8)</td>
</tr>
<tr>
<td>Dose 1 (200 mg; N=5)</td>
<td>12.6 (1.9)</td>
<td>8.0 (2.9)</td>
</tr>
<tr>
<td>Dose 2 (400 mg; N=31)</td>
<td>8.9 (4.7)</td>
<td>8.2 (2.9)</td>
</tr>
<tr>
<td>Dose 3 (600 mg; N=24)</td>
<td>9.8 (4.1)</td>
<td>7.0 (2.7)</td>
</tr>
<tr>
<td>Dose 4 (800 mg; N=40)</td>
<td>8.1 (4.1)</td>
<td>8.8 (2.7)</td>
</tr>
<tr>
<td>Risperidone (N=117)</td>
<td>8.6 (4.1)</td>
<td>8.3 (2.9)</td>
</tr>
<tr>
<td>Dose 1 (1.5 mg; N=7)</td>
<td>11.9 (2.1)</td>
<td>6.0 (2.2)</td>
</tr>
<tr>
<td>Dose 2 (3 mg; N=43)</td>
<td>9.3 (4.3)</td>
<td>8.1 (2.9)</td>
</tr>
<tr>
<td>Dose 3 (4.5 mg; N=30)</td>
<td>8.0 (3.7)</td>
<td>8.5 (2.8)</td>
</tr>
<tr>
<td>Dose 4 (6 mg; N=34)</td>
<td>7.7 (4.2)</td>
<td>9.0 (3.0)</td>
</tr>
<tr>
<td>Ziprasidone (N=60)</td>
<td>8.8 (4.6)</td>
<td>8.1 (3.5)</td>
</tr>
<tr>
<td>Dose 1 (40 mg; N=2)</td>
<td>8.5 (2.1)</td>
<td>5.5 (2.1)</td>
</tr>
<tr>
<td>Dose 2 (80 mg; N=19)</td>
<td>9.2 (5.4)</td>
<td>8.1 (3.6)</td>
</tr>
</tbody>
</table>
Dose 3 (120 mg; N=16) 9.6 (5.1) 7.6 (4.0)
Dose 4 (160 mg; N=23) 7.9 (3.6) 8.7 (3.2)

aDose information was missing for one participant

bDose information was missing for three participants

11.3.3 Side Effects and Amotivation

Clinical ratings of severity of sedation were not associated with degree of motivational deficit ($r = -0.02, P = 0.63$). Ratings of akinesia were however weakly, though statistically significantly, related to level of motivational deficit ($r = -0.10, P = 0.02$); however, prospective changes in motivation were not related to changes in akinesia ratings ($r = -0.07, P = 0.16$). Severity of extrapyramidal symptoms were also weakly, but statistically significantly, associated with severity of amotivation ($r = -0.15, P = 0.001$); however, like the relationship with akinesia, prospective changes in extrapyramidal symptoms were not linked to changes in motivation ($r = 0.02, P = 0.72$).

11.3.4 Antipsychotic Dose and Amotivation

For each antipsychotic drug evaluated, dose did not emerge as a significant factor affecting level of motivation after 6 months of treatment (olanzapine: $F_{3,147} = 1.62$, $P = 0.19$; perphenazine: $F_{3,81} = 1.15$, $P = 0.34$; quetiapine: $F_{3,93} = 1.80$, $P = 0.15$; risperidone: $F_{3,106} = 1.25$, $P = 0.30$; ziprasidone: $F_{3,53} = 0.27$, $P = 0.85$; Figure 11-1). This analysis was repeated excluding individuals receiving the lowest dose, as the number of individuals in this group was relatively small (Table 11-2), and still dose of antipsychotic was not a significant predictor of level of motivation (all $P$s > 0.05). Adding sedation, akinesia or extrapyramidal symptoms to the model as a covariate did not alter the results (all $P$s > 0.05). Thus, antipsychotic dose was not a significant determinant of amotivation.
Figure 11-1. Level of motivation stratified by dose for each antipsychotic drug: (a) olanzapine, (b) perphenazine, (c) quetiapine, (d) risperidone, and (e) ziprasidone

Higher score on this measure denote greater motivation, or less deficits therein. Error bars denote standard deviations.

Furthermore, prospective changes in level of motivation from 6 to 12 months were not related to changes in antipsychotic dose for any antipsychotic medication (all $P$'s > 0.05), even after adjusting for longitudinal changes in positive symptoms (all $P$'s > 0.05). These results remained even when restricting the analyses to include only individuals who received a dose change (N = 102; all $P$'s > 0.05).

Next, we repeated the above analysis examining the effect of antipsychotic dose on amotivation, but utilized a measure of social amotivation derived from the PANSS. The results of this analysis were consistent with those found with the other motivation measure, namely dose did not emerge as a significant factor affecting level of social amotivation after 6 months of treatment (olanzapine: $F_{3,147} = 0.11$, $P = 0.95$; perphenazine: $F_{3,81} = 0.82$, $P = 0.49$; quetiapine: $F_{3,93} =$
1.32,  \( P = 0.27 \); risperidone: \( F_{3,106} = 1.24, \ P = 0.30 \); ziprasidone: \( F_{3,53} = 0.51, \ P = 0.68 \); Figure 11-2). This remained so even after excluding the relatively small number of individuals receiving the lowest dose (all \( P's > 0.05 \)).

Figure 11-2. Level of social amotivation stratified by dose for each antipsychotic drug: (a) olanzapine, (b) perphenazine, (c) quetiapine, (d) risperidone, and (e) ziprasidone

Higher score on this measure denote greater severity of motivational deficits. Error bars denote standard deviations.

11.3.5 Initiating Antipsychotic Treatment

At baseline, 121 individuals reported not receiving any antipsychotic medication and had both baseline and follow-up motivation data. We examined whether there was any change in level of motivation after these individuals received antipsychotic medication for 6 months. Going from an antipsychotic-free state to longer-term (i.e., non-acute) treatment with antipsychotics did not result in a significant change in the degree of observed motivational deficits (\( F_{1,120} = 1.02, \ P = \)
In fact, there was a nominal increase in motivation, rather than decrease (score at baseline = 7.4, SD = 4.1; score at follow-up = 8.3, SD = 4.1). This remained the case for each individual antipsychotic examined; 6 months of treatment with olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone did not significantly change level of motivation (all $P$'s $> 0.05$).

Figure 11-3. Change in level of motivation from an antipsychotic-free state (baseline), and after 6 months of antipsychotic treatment (follow-up)

(A) Level of motivation as measured by the Quality of Life Scale is plotted, where higher scores denote greater motivation. (B) Level of social amotivation as measured by the Positive and Negative Syndrome Scale is plotted, where higher scores denote greater amotivation, or less motivation. Error bars reflect standard error of the mean.

Adding age, sex and prospective change in positive symptoms into a repeated measures analysis of variance model did not alter the findings; there was no change in level of motivation after 6 months of antipsychotic treatment ($F_{1,115} = 0.12, P = 0.73$). This remained true for each antipsychotic medication examined (all $P$'s $> 0.05$).
We also examined changes in social amotivation after these antipsychotic-free individuals received medication for 6 months. The results here too were consistent with those found with the other motivation measure; receipt of antipsychotics did not result in a significant change in the severity of social motivation deficits ($F_{1,118} = 3.80$, $P = 0.054$; Figure 11-3B). Though a trend for change was observed for social amotivation, the direction of change denotes improvement in motivation rather than worsening (score at baseline = 9.3, SD = 3.3; score at follow-up = 8.8, SD = 3.1). Adding age, sex and prospective change in positive symptoms into a repeated measures analysis of variance model did not alter these findings; there was no change in social amotivation scores after 6 months of antipsychotic treatment ($F_{1,115} = 0.03$, $P = 0.86$). This remained true for each antipsychotic medication examined (all $P$’s > 0.05).

11.4 Discussion

The present study examined whether higher antipsychotic doses, given chronically, were linked to greater deficits in motivated behaviour. We failed to find such a relationship. Though previous studies have linked antipsychotics with sedation (254), this too was not related to degree of amotivation in this investigation. Finally, chronic treatment with antipsychotics did not prospectively diminish motivation compared to baseline in individuals who were antipsychotic-free. The present findings therefore argue against the notion that antipsychotic drugs cause or worsen amotivation in patients with schizophrenia.

Though some previous work has linked antipsychotics to aberrant reward-system functioning (1162), more recent findings suggest that these medications may actually improve functioning within this circuit (1164, 1300). This seems at odds with previous studies demonstrating that acute (i.e., single) doses of antipsychotics negatively affect motivation and reward processing (496, 497). The present study only examined relatively chronic effects of antipsychotics (i.e., differences in motivation after 6 months of treatment), and therefore cannot speak to the relatively acute effects of antipsychotics and potential differences in findings therein. Nonetheless, the present study does demonstrate a lack of effect of chronic antipsychotic treatment on motivation. This raises the question as to why there is discrepancy in effects of acute and chronic dosing. We speculate that several factors might be involved. First, individuals may habituate to the sedative effects of these medications, a process which could involve...
compensatory (neurobiological) changes. Second, it is possible that antipsychotics bias the type of goals that treated individuals pursue, and that although motivated behaviour in general is not altered, underlying processing of reward attributes is altered causing a shift in goals being pursued. This should be directly tested in future work.

The mechanism(s) that might underlie our findings of chronic treatment with antipsychotics not undermining motivation remain to be elucidated. As the majority of pre-clinical studies examining the effects of antipsychotics on motivated behaviour have employed acute dosing paradigms, parallels to the present study, and indeed real-world practice, cannot be drawn. We can nonetheless speculate as to some potential candidate mechanisms. One such mechanism involves habituation or the development of tolerance to antipsychotic medications. There is in fact several pre-clinical studies that have documented tolerance-like effects after chronic exposure to antipsychotics (1301), while other studies have documented that the acute and chronic effects of antipsychotics are distinct both behaviourally and neurobiologically (1302). These effects have been linked to both increased number of dopamine D2 receptors (1301), as well as increased sensitivity of the receptors (1299). Increased dopamine D2 receptor expression outside the context of antipsychotics has in fact been linked with increases in goal-directed behaviour (1303). Clinically, the number of dopamine D2 receptors has been suggested to be slightly increased in medicated patients with schizophrenia, a finding that is not observed in antipsychotic-naive individuals (316). It should be underscored that these findings have not been linked to motivated behaviour per se, and as such future pre-clinical work should first examine whether chronic, rather than acute, antipsychotic exposure is linked with motivational deficits, and second determine potential neurobiological mechanisms underlying this plasticity.

Motivation is a multi-faceted construct encompassing multiple underlying and overlapping, yet distinct, processes (881, 882). The two measures used in the present investigation evaluate subjective reports of drive and behavioural output as it relates to the pursuit of goals, including social interactions in the case of the PANSS social amotivation measure. These measures however do not disengage the precise processes that ultimately manifest as goal-directed behaviour or “motivation.” In fact, across studies clinical ratings of amotivation have been found to be related to a number of reward processes including for example effort cost computations (904, 1221, 1222, 1255), and reinforcement learning (1052, 1304). It is important to move beyond examining effects of various variables, in our case the effect of antipsychotic medication,
on “motivation” more broadly defined toward examining these effects on underlying subprocesses, ideally evaluating multiple reward-related components concurrently. Though several recent studies have examined specific reward processes, few, to our knowledge, have examined multiple processes within the same subjects. It would be valuable to know whether chronic antipsychotic treatment differentially affects certain approach-related behaviours while sparing others; pre-clinical studies are well positioned to answer such questions.

The present results do not refute the existence of antipsychotic-induced adverse effects such as akinetic extrapyramidal symptoms, which have long been linked to treatment with these mediations (486). However, the present results suggest that such akinesia is only weakly linked with motivation, at least as evaluated in the present study (i.e., the initiation and pursuit of goals). It is also interesting to note that akinesia is present in antipsychotic-naive patients with schizophrenia and in these individuals linked with higher negative symptom burden (484). This relationship, observed before initiation of antipsychotics, suggests that akinesia itself is not solely an iatrogenic feature of the illness, and may obfuscate attempts to identify drug-induced side effects, especially secondary negative symptoms.

A strength of the present investigation is its examination of dose across multiple antipsychotic drug types, including conventional as well as atypical, but doing so individually rather than collapsing across medications and using a crude conversion (e.g., chlorpromazine equivalents). At the same time, the present study has several limitations that should be mentioned. First, our first set of analyses was restricted to dose of antipsychotic received, rather than plasma or brain levels. Future studies would be well positioned to replicate and extend the findings presented herein to examine more proximal effects of antipsychotic drugs, using for example position emission tomography. Second, medication dosing was not assigned randomly, but rather determined based on real-world clinical decisions, a limitation shared by naturalistic investigations and empirical studies employing fixed, flexible dosing. Third, as motivation was not assessed directly following initiation of antipsychotic medication (i.e., within a few days), we were not able to directly contrast acute and more chronic treatment with these drugs; nonetheless, our results hold for the latter. Fourth, the analysis examining the effect of initiating antipsychotics was carried out in a drug-free, but previously treated, population rather than in antipsychotic-naïve individuals. Fifth, the measure of motivation employed involved both patient self-report and clinician judgment, rather than objective assessment. Given the importance of
motivational deficits, especially in terms of functioning (685), it is imperative that future studies
determine the effect of chronically administered antipsychotic medication on objective
behavioural assessments of goal-directed motivation (e.g., effort-based decision making), ideally
employing longitudinal designs. Last, our analysis included only 5 medications. Although these
spanned both typical and atypical agents, it remains possible that specific antipsychotics not
examined here, have an effect on motivation. Related to this point, the present study did not
include very high doses, but rather included doses reflective of current practice.

It has long been held that antipsychotic medications can produce secondary negative symptoms
(487, 488, 519), which in turn can exacerbate primary negative symptoms. Amotivation is
considered an important feature of these symptoms; however, the present study did not find
evidence that these medications when given over a longer period of time diminish motivation.
Moreover, we failed to find a dose-dependent relationship between antipsychotics and
amotivation. Our findings raise the possibility that individuals may habituate to, at least some of
the side effects of these medications, and that these medications do not necessarily undermine
goal-directed motivation. It should be noted that we found no evidence that a larger amount of
antipsychotic received was associated with greater amotivation, but by the same token we also
did not find evidence that higher doses of antipsychotic promote motivation, suggesting that
novel treatments targeting different mechanisms are needed for these impairments.
Chapter 12

12 General Discussion

12.1 Summary of Results

The studies reported in the preceding chapters sought to individually and collectively advance the understanding of motivation deficits present in people with schizophrenia. To this end, several research questions were proposed to examine specific aspects of motivation and their importance and relevance in schizophrenia. Topics examined included the prognostic value of motivational deficits for predicting functional outcomes (Chapters 3 and 4), their prevalence in young early-course patients (Chapter 4), evaluation of clinical rating scales that measure this domain (Chapter 5), elucidation of underlying reward processing mechanisms (Chapters 6 and 7), evaluation of the reliability and validity of an objective measurement tool (Chapter 8), examination of inter-relationships with cognitive performance (Chapters 9 and 10), and finally an exploration of the influence of antipsychotic medications (Chapter 11). The results of these investigations provided several advances and clarifications of the construct of amotivation in schizophrenia.

The first study provided evidence for the prognostic importance of motivational deficits in patients with early schizophrenia, where this domain of psychopathology demonstrated the largest and most reliable prediction of concurrent outcomes. Other variables did not contribute any incremental predictive value once these deficits were accounted for, underscoring the critical association between motivational deficits in particular and outcome. These results were largely replicated in study two, where a larger and broader sample of early schizophrenia patients was examined. Here too, motivational deficits emerged as the most robust and reliable predictor of not only cross-sectional but also longitudinal outcomes. Consistent with the findings in study one, once motivational deficits were accounted for in our models, other variables failed to offer any incremental predictive value. In contrast, even after accounting for a host of known predictors of outcome, motivational deficits provided significant incremental predictive value for the determination of outcome. Variables such as positive symptoms and neurocognition together accounted for approximately 20% of the variance in outcomes, and motivational deficits added
predictive value over and above this in the range of approximately 30% explained variance. Beyond predictions of outcome, this study also provided evidence that changes in motivational deficits were linked to changes in functional outcomes, providing initial evidence for a possible causal relationship. Such a longitudinal relationship was not seen with neurocognition, raising the possibility of a specific causal link.

Beyond highlighting the prognostic value of motivational deficits for the determination of functional outcomes, study two also documented the prevalence of motivational deficits in a relatively large and diverse sample of early-course schizophrenia patients, who did not have significant depressive or extrapyramidal symptoms. Approximately 15% of patients experienced severely debilitating motivational deficits, while a significantly higher proportion experienced some degree of impairment in this domain (up to 76% of patients). These rates were similar to those found in the follow-up visit; approximately 12% of patients had severe motivational deficits, and 75% experienced some degree of motivational impairments. Moreover, there was no significant or substantial change in motivation following treatment, highlighting the persistent nature of these deficits. That these deficits are highly prevalent and persistent, even in the early course of the illness, in conjunction with our results showing their robust association with future outcomes, highlights the scope of the issue; motivational deficits represent an area of unmet medical need.

Study three provided empirical evidence for the convergence of several commonly used motivational deficit scores derived from different instruments. This serves as an important bridge for comparing findings from studies using different instruments to quantify motivational deficits, including studies included in this thesis. This study also demonstrated the relative independence of motivational deficit scores from other clinical variables. Among these was dose of antipsychotic medications, where we found no relationship between this variable and severity of amotivation. This raises the possibility that there does not exist a systematic dose-dependent relationship between antipsychotic medications and burden of motivational deficits. We return to this possibility in study nine.

In study four we examined motivational deficits more objectively, analogous to the approach taken in the pre-clinical literature, where motivation is defined as an animal's willingness to expend effort in pursuit of some reward. While there are several such examinations currently
reported in the literature, including several cited in this thesis, at the time we designed and began this study, there were no such published reports. Even still, our study stands alone in the examination of younger early-course patients. In study four, we found evidence for incentive motivation deficits in patients with schizophrenia using a laboratory performance-based measurement tool; specifically, we found that patients were less willing to expend effort in pursuit of valued rewards, in our case money, than were matched healthy control participants. Beyond providing objective behavioural evidence for motivational deficits in patients, this study provided initial clues to the computational processes underlying such deficits. We found that patients reported subjectively valuing the rewards to a similar degree as controls, ruling out the assertion that these impairments simply reflect patients working less because they don't want the outcome. Rather, in evaluating the cost versus benefits of exerting effort, we found evidence supporting the idea that the abnormality in schizophrenia might lie in the computation of effort costs. Study five builds on this work suggesting that patients with schizophrenia might have impairments in their ability to compute effort demands required to pursue actions in order to obtain outcomes. Specifically, study five, which included a larger sample of patients than study four, examines several other competing hypotheses, including the possibility that patients' lack of motivation reflects their inability to learn that certain cues or actions are associated with outcomes. Considering several other reward processes, we continued to find support for the notion that there exists impairment in effort cost computations in patients with schizophrenia. This computational abnormality was related to both the severity of clinical motivational deficits and functional status.

Studies four and five employed an objective performance-based assessment tool to measure motivational deficits in a laboratory setting. Such an approach is akin to how neurocognitive impairments are routinely evaluated in a neuropsychological setting in patients with schizophrenia. In study six, we explored the psychometric properties of an effort-based decision making paradigm that we optimized for use in patients with schizophrenia. We found evidence for good reliability of the measure, including test-retest reliability, with reliability metrics within the range of commonly used performance-based cognitive tests. While effort performance was related to some motivational indices (e.g., differences in deficit syndrome patients), indicating some degree of convergent validity, the overlap was not robust, which we interpreted as suggesting divergence in the focus of performance-based and clinical interview-based measures.
of amotivation. The former possibly reflects a variable more proximal to underlying pathology. All together, study six found support of good psychometric properties of the effort-based decision making task examined. This tool may be used to evaluate therapeutic efficacy of interventions specifically targeting motivational deficits in the future.

In study seven, we turned to the examination of the inter-relationship between motivational deficits and other domains of psychopathology present in schizophrenia. In particular, we evaluated the association between motivation and performance on cognitive tests. In this study, we found that patients’ performance on a battery of cognitive tests was significantly associated with their motivation to complete the aforementioned tests. One interpretation of this association is that patients who are not motivated, or do not value or have no interest, in completing the cognitive tests generally have poor performance. In any case, this finding raised the possibility that cognitive tests were not assessing maximal performance in the same manner as they were intended to. Study eight was carried out to replicate and extend the findings from study seven. In this study, we examined the inter-relationship between motivational deficits and cognitive test performance in a large sample of stable patients with schizophrenia. Again, we found evidence for a significant relationship between these two variables, with greater motivational deficits being associated with poorer performance on cognitive tests. This relationship was pervasive and existed for each cognitive domain evaluated, and could not be fully accounted for by a third variable such as severity of other symptoms or functional status. Beyond cross-sectional relationships between motivation and cognition, we also found evidence for significant longitudinal inter-relationships, such that increases in motivation over time were associated with greater improvements in cognitive test performance. These findings highlight the potential influence of motivation on cognitive test results.

In study nine, the final study presented in this thesis, we examined the issue of secondary negative symptoms, and specifically whether antipsychotic medications caused a worsening of motivational deficits. No evidence for a dose-dependent relationship between dose of antipsychotic received and burden of motivational deficits was found in a large sample of patients with schizophrenia maintained on selected antipsychotic medications. In a subgroup of patients who were antipsychotic-free, and subsequently treated with antipsychotic medications, we found no evidence for a change, let alone worsening in the severity of motivational deficits. These findings suggest that antipsychotics, when administered chronically, do not necessarily
lead to a worsening of motivational deficits in schizophrenia. Such results also challenge the longstanding notion that (chronic) dopaminergic blockade necessarily reduces effortful goal-directed behaviour.

12.2 Clinical Implications

Several of the findings reported in the preceding chapters have implications for the clinical care of individuals with schizophrenia. However, as specific treatments or methods of care were not systematically evaluated and compared to one another, as would be the case for randomized controlled trials for example, we can only make speculations as to what the clinical implications of our studies might be. That is to say that, unfortunately, our findings do not lend themselves to immediate translation into recommendations for changes in clinical care. Nonetheless, several notable findings would be of interest to clinicians.

Clinicians should be aware that most patients with schizophrenia, even those who are younger and have not been chronically ill, experience impairments in their motivation. These motivational deficits are persistent, and treatment with antipsychotic medications does little to affect these symptoms. Further to this point, it should be underscored that antipsychotic medications fail to substantially improve or worsen these symptoms. That is to say, patients' motivational deficits are not merely an iatrogenic side effect of treatment with antipsychotic medications.

For those wishing to quantify motivational deficits in the context of routine clinical practice, our findings from study 3 are of relevance. In that study, we found a high degree of convergence between several measures of motivational deficits, suggesting that each is tapping into the same underlying construct. Therefore, any one of the motivational measures could be utilized, including the single-item measure derived from the Quality of Life Scale, which can serve as a quick subjective measure.
12.3 Broad Limitations

As with all endeavors, including scientific pursuits, there are advantages to taking a particular approach, but also certain limitations. While the limitations of each individual study have been briefly mentioned in the discussion sections of the respective chapters, some additional specific as well broader limitations of the investigations undertaken will be addressed here.

All investigations report results that included patients both willing and competent to provide informed consent for their participation in the respective studies, which is consistent with ethical principles for conducting human research, as outlined in the most recent iteration of the Declaration of Helsinki (1305). Both willingness and competency to participate in research limits the possible range of participants that are eligible and ultimately included in research studies. While this has been enforced for good ethical reasons, it does nonetheless limit the generalizability of our findings. This is particularly salient in a thesis dedicated to issues pertaining to motivation. That is, we are studying motivational deficits among patients that are both willing and competent to participate in research, and complete the sometimes lengthy and tedious testing procedures. It is remarkable that even after excluding individuals who are not "motivated" to participate in research, we still observe (sometimes severe) motivational deficits in the patients that we do evaluate.

Many of the associations from which we drew inferences were based on results that were associational in nature. While limited in our ability to draw concrete conclusions about casual relationships, our results do, at any rate, highlight an association which is interpreted in a pre-existing or a priori conceptual framework. For example, in our studies seven and eight we find a relationship between motivation and cognition. Pragmatically, and perhaps even theoretically, this result can be interpreted in at least three ways: 1) motivation impacts cognition; 2) cognition impacts motivation; or 3) both motivation and cognition are impacted by some other "third" (i.e., confounding) variable. The evidence for option 3 is most limited given our robust findings in study eight ruling out the possibility of several potentially confounding variables; nonetheless, this still remains a possibility as we did not include an exhaustive list of variables to control for or statistically adjust. Options 1 and 2 seem perhaps equally likely. But, we emphasize option 1 for several reasons. Perhaps chief among these is face validity and intuitive appeal. It seems rational to conjecture that performance on a given cognitive test does not represent participants'
absolute maximal ability, especially in an illness associated with not only motivational deficits but also motor retardation, both of which could, at least theoretically, undermine participants' ability or willingness to execute maximal effort and motivation to complete cognitive tests.

Future work manipulating very specific variables may be better able to parse the directionality of such associations.

Our assessment of motivation relied on a combination of self-reports, clinical interviews and behavioural output. Spanning both subjective and objective measurements, our investigations had the strength of eschewing potential conceptual overlap between functioning and motivation (when assessed subjectively) in some cases, while minimizing biased reporting when examining computational processes (assessed objectively). Nonetheless, these represent only selected methods of assessment. We did not, for example, examine motivational processes from a neurobiological standpoint using neuroimaging techniques, a point that will be addressed further later in this chapter in the context of future directions. Incorporating these multiple levels of analysis has the potential to provide robust converging evidence addressing a certain topic, and at the same time pointing towards mechanisms.

When evaluated using self-report or clinical interview based measurements of motivational deficits in schizophrenia, we have considered this variable as a unitary construct. Just as research has shown that the broader construct of negative symptoms is, in fact, a compilation of multiple subdomains, one of which is motivational deficits, it may be the case that what we have considered as a single construct may instead reflect a constellation of multiple underlying constructs. While we examined several reward processing variables in studies four and five, which are all theoretically linked to motivation (i.e., goal-directed behaviour), such an analysis falls short of examining the many other (possible) facets of motivation. Studies included in this thesis tap into intrinsic and extrinsic motivation, as well as variables that combine the two. Our studies do not however shed light on the specific nature of the role of one versus the other type of motivation or, for that matter, we do not consider variations in goals as a potential contributor to individual differences in goal-directed behaviour. Decisions to pursue certain actions are done at the expense of some counterfactual or alternative, and it is certainly reasonable to surmise these alternatives will shape and influence decision making. Understanding human motivation is a complex enterprise; adopting multiple frameworks may provide the nuanced and intricate approach needed to understand its many aspects. Along these lines, and as alluded to in the
Introduction, we have mainly considered motivation from a behavioural neuroscience perspective of reduced goal-directed behaviour, including subjective accounts of this. However, there are a number of other complementary approaches including the examination of physiological responses to passive behaviour.

Most of the included studies examined motivational deficits in young adults with schizophrenia, who have been ill for only a few years on average. This represents a strength in our approach, as it avoids possible confounding effects of a chronic illness, and thus provides evidence of the presence and importance of motivational deficits in the very early stages of the illness. However, our approach does not provide insights into the onset and course of these deficits. While motivational deficits have been reported in individuals in the putative prodrome, before the onset of psychosis, the nature and mechanisms of these deficits remain unclear. Also unclear is the extent to which these deficits are confounded by other psychopathological domains (e.g., depressive symptoms) in the prodrome, or whether these deficits remain stable following the onset of psychosis. It also remains uncertain whether motivational deficits might perhaps worsen or evolve over the course of the illness, which speculatively might be related to environmental restrictions.

In our studies of reward processing mechanisms of goal-directed behaviour (studies 4 and 5), we worked within a framework adapted from both pre-clinical behavioural neuroscience investigations as well as field-consensus (i.e., the RDoC). That is, our investigations evaluated distinct reward processes that have been demarcated and classified as unique in prior work. In doing this, a limited number of processes were identified (e.g., reward valuation, effort cost computations, reward learning). However, this is almost certainly an oversimplification of the "true" scenario of how animals, including humans, process, integrate, and respond to reward information. For example, what we consider reward valuation can hypothetically be deconstructed into the hedonic and emotional initial reaction to reward attainment, the cognitive processes that contribute to non-immediate sustaining of the initial reaction, as well as the memory encoding and retrieval processes that might contribute to or impact either of these. For the sake of parsimony (1306), we consider only a selected group of key reward processes. Whether these hypothetical sub-subprocesses of reward exist and/or are dissociable, and indeed whether these contribute to our understanding of motivational deficits in schizophrenia, remains to be seen.
In studies 4 and 5, a case-control experimental design was employed to examine whether individuals with schizophrenia (cases) differed on selected measures versus individuals without schizophrenia (controls). The case-control design is grounded in the assumption that cases contain the variable of interest, while the controls do not (1307, 1308). In our case, this was a diagnosis of schizophrenia. However, inferences about group differences between cases and controls requires that the 2 groups do not systematically differ on any other variable. That is, the groups should be "matched" with regard to all other variables of no interest (1309). If this condition is not met, we risk faulty inferences about any potential group differences relating to our variable of interest, where they may, or possibly may not, be related to some other factor. This is a particularly difficult condition to meet when comparing individuals with a psychiatric diagnosis with those without one, as the former group is likely to harbour a range of variables that systematically make them different than non-psychiatric healthy controls. In patients with schizophrenia there are several examples of such factors including smoking status, metabolic dysfunction, and personal socioeconomic status, to name only a few. In our studies, these variables were not fully accounted for. Therefore, it is possible that our inferences relating to patient versus control differences on our variables of interest are, instead, related to some confounding variable, instead of something inherently linked to schizophrenia. Nevertheless, our findings do hold for the individuals included in our investigations, and do demonstrate differences among individuals with schizophrenia versus healthy participants drawn from the general community.

Not all patients who qualify for the diagnosis of schizophrenia, or even schizoaffective disorder for that matter, evidence impairments in motivation. Certainly those who experience severe motivational deficits represent only a minority of cases. This is not such a revelation though, as motivational deficits are not a core diagnostic feature in nosological texts such the DSM or ICD, where positive psychotic symptoms are emphasized (see Introduction for a discussion). Despite the focus on psychosis for establishing a diagnosis of schizophrenia, it is perhaps remarkable that so many individuals also demonstrate significant impairments in motivation. Nonetheless, because all patients with schizophrenia do not manifest this symptom, it cannot be taken to be characteristic of all patients, or pathognomonic, as it is also present in a host of other psychiatric and non-psychiatric (e.g., neurological) illnesses (931). Whether motivational deficits in schizophrenia simply reflect a marker of illness severity or serve as an indicator of poor outcome
(i.e., motivation as a quantitative trait) or, instead, if patients with and without these symptoms represent distinct forms of the illness with disparate underlying pathophysiology (i.e., motivation deficits as a qualitative trait) remains to be established. Some work using the deficit syndrome construct for which prominent, primary and enduring motivational deficits (e.g., diminished sense of purpose) are a diagnostic criterion has provided evidence for the latter (520). For example, those with prominent negative symptoms seem to form a distinct taxon within the broader diagnosis of schizophrenia (1310, 1311); while other work supports the dimensional, rather than categorical, view of these symptoms (681). At present, the existing evidence does not conclusively support (or rule out) any one of these positions.

12.3.1 What is Schizophrenia?

The work presented in this thesis is predicated on the notion that schizophrenia is a valid and reliable construct. While the reliability of the diagnosis is generally very high (1312), especially when made using standardized structured instruments, the question of validity remains. Exactly what is schizophrenia? Although countless texts, including textbooks, research articles, and review papers, have been written on the topic, some fundamental questions remain unanswered. One recent review paper, aimed at consolidating the knowledge accrued over the years about schizophrenia by reviewing any and all systematic reviews focusing on schizophrenia, concluded that "while our knowledge of schizophrenia is very substantial, our understanding of it remains limited" (1313). This is a telling commentary regarding the lack of fundamental understanding of what exactly schizophrenia is.

In the early 1980's a series of short essays were written that asked authors to write down the crux of what they considered to be schizophrenia, and the responses were notably divergent, with each focusing on different aspects and most conceding that a cohesive definition remains elusive (1314-1320). One particular question that remains unanswered is whether schizophrenia represents a single disease entity, or whether there exist several unique diseases under the syndrome of schizophrenia (1321-1325). This perhaps stems from the (sole) reliance on phenomenology to establish diagnoses. At any rate, this thesis does not intend to provide any special answers to this long-held question. Rather, the possibility that our investigations are
based on multiple diseases, and that different results may have emerged with the inclusion or exclusion of only a subset of these, must be acknowledged.

One indicator of the validity of diagnosis is its separation from other conditions. As alluded to in the Introduction (Chapter 1), there exist several schizophrenia-spectrum conditions, including for example schizoaffective disorder, which share many features with schizophrenia per se, but are relegated to their own unique diagnostic categories. The schizophrenia-spectrum is quite broad, and may include latent forms of illness that do not qualify for a psychiatric diagnosis (1326-1330). This was acknowledged by both Kraepelin and Blueler in their early descriptions of schizophrenia (14, 23, 25). Therefore it is critical to exclude such cases in case-control studies comparing individuals with schizophrenia versus those without schizophrenia; otherwise, there is a risk of contamination of the latter sample. In the studies included in this thesis that recruited a healthy comparison group, we employed several strategies to this end, including the exclusion of individuals who expressed even subclinical manifestations of schizophrenia-like (i.e., schizotypal) traits. However, whether these individuals might have harboured clinically unmanifested schizophrenia liability (i.e., endophenotypes) is unknown (1331-1333).

12.4 On Doing "Good" Schizophrenia Research

Schizophrenia is a complex disease that affects many facets of human experience. It would be naive to surmise that tackling any one aspect without full regard to the broader picture will make leaps in our understanding of the illness. Indeed, essays have been written highlighting the need for a multidisciplinary and multi-level analysis of schizophrenia (1334, 1335). The work presented in this thesis, unfortunately, falls short of this, as it focuses almost entirely on subjective and behavioural measurements of motivation, as well as clinical assessments of other domains of psychopathology relevant to schizophrenia. Our studies do not, for example, link the subjective and behavioural measurements of motivation to underlying neurobiological mechanisms including brain functioning, molecular biology, or genetics. Such work is left to the future. The hope nonetheless remains that the work included in this thesis has laid the groundwork for the development and testing of unifying theories of schizophrenia, or at least for the development of future studies that will contribute to such theories. In the end a unifying
theory with testable predictions, and falsifiable hypotheses, is the backbone of scientific inquiry (1336-1338), in contrast to the pursuit of facts purely for their own sake (1339, 1340).

12.4.1 A Tentative Theory

Theories should provide an integrated framework from which to interpret empirical findings, as well as provide a basis to articulate well-formed predictions and falsifiable hypotheses. Here, such an attempt, albeit admittedly preliminary in its conception, is made. Aware that speculative theories and models are inherently incorrect, it is hoped that such a proposition might prove useful in moving the field forward (1341). There are several examples of solid theories that have withstood the test of time, including those that have attempted to link aberrant neurobiological functioning, psychological processes, and symptoms. For example, there are proposals that at least a subset of positive psychotic symptoms of schizophrenia stem from an underlying dopaminergic abnormality that manifests in the psychological realm as an aberrant inappropriate assignment of salience to environmental cues (321, 1342-1346). Though various iterations of this theory exist, it primarily relates to the positive symptoms of schizophrenia, with only minimal reference to other aspects of the illness. Here, such a "narrow" theory is proposed to account for the negative symptoms of schizophrenia, and motivational deficits in particular, and no attempt is made to cover all aspects of schizophrenia and its associated features (1347). Instead, an attempt is made to be relatively concise, leaving open the possibility for further elaboration in the future.

There exists several proposals for the mechanisms underlying negative schizophrenia, each varying in focus and in their ascription of these symptoms to either underlying pathology or psychosocial factors (1348). One theory has proposed that the motivational deficits of schizophrenia stem from a computational abnormality related to the "representation of (expected) value," and that this computational abnormality is associated with deficits in prefrontal functioning, specifically within the OFC, and may be mediated by dopaminergic activity (883). Some of basic theoretical tenets of this theory remain inadequately described though; for example, it is unclear whether this theory implies a fundamental impairment in the representation of value per se, and/or whether the impairment lies in the use of this signal to guide actions (i.e., the translation of the value signal to goal-directed action). In any case, this theory is expanded
upon, and the focus somewhat altered. Moreover, explicit predictions, including possible points of divergence with the aforementioned theory, as well some falsifiable hypotheses, are outlined.

We propose that the motivational deficits in schizophrenia result from a faulty integration of value-based signals that contribute to the computation of person-specific subjective values of outcomes. We hypothesize that the basic mechanisms for the computation of value (and cost) signals is intact in people with schizophrenia. However, cost-discounted value (i.e., net value or utility) signals are disrupted. There are several lines of evidence for this, including evidence that patients' in-the-moment appraisal of the value of stimuli is not impaired (1099, 1238)(Chapter 7). Evidence for intact estimation of cost in schizophrenia is relatively sparse. Taking our data from Study 5, where we asked participants how effortful they found both the "easy" and "hard" tasks, we explored whether participants' appraisal of the difference in effort for these tasks was different; we failed to find such differential effort cost estimation impairments (p>0.05). Moreover, all participants in that study correctly identified the hard trial as more effortful than the easy trial (Chapter 7). Instead of an effort cost computation per se, we instead hypothesize that the impairments in schizophrenia lie in the integration of this effort estimation signal with a valuation signal. In other words, patients are impaired in their ability to integrate these signals, which results in increased noise in their representation. This increased noise ultimately undermines the appropriate use of this signal to guide actions. This proposal is somewhat different than the proposal of a value representation deficit per se, as it proposes that the mechanisms by which patients compute value signals is, in fact, intact. However, it also heavily overlaps with the value representation theory as both proposals suggest a deficit in the representation of value, but do, however, differ in the cause of this representational deficit.

There are several conceivable ways to disentangle whether patients are impaired in their ability to integrate costs and benefits or whether their impairments lie in the representation of value signals. One manner in which to do this would be to through study design. An experiment could be designed where individuals with schizophrenia are compared to a group of healthy control subjects, who are matched on working memory capacity (i.e., an index of representational ability). We should acknowledge that such a study design would certainly create a selection bias against many patients with schizophrenia; however, such as design would effectively control for one variable of interest. Using this design, patients and controls could be tested on some cost-benefit decision making task. If impairments are found in patients, it would suggest a
relationship with integration of costs and benefits, rather than impairments in their ability to represent value signals. Of course, other competing hypotheses would need to be ruled out concurrently (e.g., in-the-moment estimation of value). Additionally, one could examine cost-benefit decision making in four groups of patients with schizophrenia matched on clinical characteristics, but selectively different on working memory capacity on the one hand and motivational deficit severity on the other. Such an experiment would provide insights into whether cost-benefit integration is impaired as a function of motivational deficit severity, and further whether this has any interactions with representational ability, or whether such deficits are independent of this variable.

Several pre-clinical investigations have been carried out to map the neural circuitry underlying cost-benefit decision making (see Chapter 1 for details). We propose that in schizophrenia this faulty cost-benefit integration is related to dysconnectivity within the human reward system network, including hubs within the ventral striatum, anterior cingulate cortex, and parts of the prefrontal cortex, including the orbitofrontal cortex. We emphasize dysconnectivity rather than simple hyper- or hypo-functioning within any one of these regions, although such regional abnormalities may be associated with network level dysconnectivity. Such dysconnectivity is likely mediated by a host of neurotransmitters, including glutamate and GABA, but most relevant to our proposal is probably dopamine. We figure a key role for dopamine signaling abnormalities in contributing to the neural dysconnectivity that undermines effective cost-benefit integrations. Previous work has implicated dopaminergic transmission in efficient neural network configuration (1349) and functional connectivity between nodes within the reward system (1350-1355). In terms of phenomenology, such faulty integrations of computational signals undermine clear and accurate decisions to pursue and persist in goal-directed behaviour. This possibility also has subjective consequences as well, which may manifest as lethargy.

Our preliminary theory therefore proposes that abnormalities in dopamine signaling contribute to neural dysconnectivity which undermine the accurate integration of value signals. This ultimately leads to impairments in real-world goal-directed behaviour and the subjective experience of apathy. However, much of this proposal draws on disparate lines of evidence, and direct evidence linking these variables in schizophrenia is lacking. In fact, there are no published studies that have examined effort-based decisions and their neural correlates in schizophrenia, though at the time of this writing several preliminary investigations were underway.
Support for our proposal comes from several previous investigations, including work showing that motivational deficits are linked to abnormalities in basal dopamine levels within the ventral striatum (763), as well other evidence linking severe negative symptoms, in the context of the deficit syndrome, to abnormal neural network properties (1356). However, evidence linking these variables to aberrant cost-benefit decision making does not exist, though studies included in this thesis have provided at least preliminary evidence that aberrant cost-benefit decision making is associated with impairments in real-world goal directed behaviour and subjective accounts of apathy (Chapter 7).

Several findings, if found in schizophrenia, would falsify our proposal. Such findings could include a lack of relationship between cost-benefit decision making and neural dysconnectivity, or with dopamine signaling abnormalities. Such findings would suggest that other neurobiological variables are responsible for the abnormal computational processing outlined here. In this case, our theory would need to be revised or simply replaced with a more up-to-date account. Another form of evidence that would falsify our theory is if it is discovered that patients with schizophrenia do not evidence impairment in the integration of value signals. Although several studies have demonstrated abnormal cost-benefit decision making in schizophrenia, including studies included in this thesis (studies 4 and 5), it is possible that future studies employing more rigorous study designs will fail to replicate these findings.

12.5 Future Directions

Several questions germane to this thesis remain unanswered. Just as this thesis included several novel empirical studies that filled notable gaps within the literature and discretely advanced knowledge on the topic of motivation in schizophrenia, future work is needed to continue filling the remaining gaps. Here, several lines of inquiry are outlined that would fill some of these gaps.

12.5.1 Outcome Studies

Regarding our predictive models for determining functional outcome, it is notable that the amount of variance predicted was incomplete. This may relate to our inclusion of only a selected
number of predictors, as well as the focus on only clinical predictor variables. Our study 2 included a relatively comprehensive range of predictors, but it was by no means exhaustive. At this point, is it unclear whether the addition of other clinical variables might have added to the predictive value of our models; rather, what seems more plausible is that the inclusion of other more basic (neuro)-computational processing variables may add to this, though this is purely conjecture. Beyond predictive value, evaluating the association between basic processes and outcome may provide a more detailed mechanistic understanding of the factors that contribute to real-world impairments in community functioning. Our studies have demonstrated the robust and reliable association between clinically evaluated motivational deficits and functioning; however, the mechanism underlying this relationship remains uncertain. Dissecting motivation into its underlying computational processes may provide a framework that is better able to delineate the mechanism of how motivation putatively impacts functional outcomes in schizophrenia. Though our study 5 provides initial evidence that effort cost computations are involved, a more comprehensive (path-analytic) analysis is needed to tease apart specifics.

12.5.2 Assessment of Reward Processing

In studies 4 and 5, several objective paradigms were employed to tap into underlying computational processes based on our current understanding of these processes and their underlying neurobiology from the behavioural and affective neuroscience literatures. Our studies tease these computational processes apart behaviourally, but the neurobiological substrates remain unknown. We have conjectured as to the underpinnings of some of these constructs (see Chapter 1), but empirical evidence remains to be seen. Future studies examining the neural substrates of effort cost computations in schizophrenia are needed to confirm our predictions that these computational impairments are subserved by corresponding neural impairments in NAc and ACC functioning, and in particular their connectivity (881). This can be done by combining fMRI and a variant of the effort-based decision making task employed in study 5/6, and comparing fMRI-elicited BOLD activation differences between individuals with schizophrenia versus healthy control participants. The key phase of interest within the task would be the choice phase, where participants decide whether or not to expend effort for reward. The task would need to be further modified though. The current version asks participants to make a decision on each
trial, precluding an analysis of choice per se as all trials involve a choice. Trials where participants execute pre-determined trials could be added, as this effectively nullifies the choice but the prospect of effort and reward remains intact. Comparisons of BOLD activation patterns for choice trials versus (i.e., minus) predetermined-choice trials could be compared across groups. This would provide evidence, or lack thereof, of neurocomputational differences during cost-benefit decision making among patients and controls.

12.5.3 Does Motivation Impact Cognitive Test Performance?

Studies 7 and 8 provided evidence of a robust and reliable association between motivation and cognitive test performance among individuals with schizophrenia. However, the study provided evidence for just that, an association, and inferences around causal links are relegated to the arena of speculation, even if based on preconceived theoretical notions. Future studies manipulating some aspect of motivation that theoretically should not affect core cognitive processing should be conceived and carried out. This is conceptually difficult, as there is substantial overlap between motivation and cognition, including overlap in how these constructs are defined and demarcated from one another. In Chapter 1, some of this conceptual overlap was highlighted. Some of the trouble with manipulating the incentive value or motivational properties related to the cognitive testing procedure is that this effectively creates a non-standardized manner of assessment. Whether manipulations of motivational or emotional content recruit additional processes that enhance core cognitive processing, or interact with core ability, is unclear but theoretically possible. However, such studies may provide the initial steps towards resolving this issue. It could be argued, but perhaps not so convincingly, that an effective manipulation of motivation and subsequent differences in cognitive test performance is sufficient to suggest a motivational influence on cognitive test performance. An example of such a study could employ a counter-balanced within-subjects study design where participants are tested on selected cognitive tests twice. One testing session would involve cognitive testing using standardized procedures, while the other might couple performance with some incentive (or punishment) such as bonus money (or the taking away of promised money). If performance is better (i.e., higher test scores) in the incentive condition, it would lend some support to the notion that standard neuropsychological testing procedures are not conducive to eliciting maximal
performance on cognitive tests as they were designed and intended to do and, indeed, how they are interpreted. The test-retest duration would have to be sufficiently long to minimize practice effects, and order effects would have to be examined as well.

12.5.4 Clarifying the Idea of Antipsychotic-induced Motivational Deficits

The final study included in this thesis (study 9) examined the issue of antipsychotic-induced motivational deficits. It is widely held that antipsychotics, perhaps through their dopaminergic blockade properties, blunt motivational drive. Our study failed to support this hypothesis. However, there were some notable limitations to our approach, some of which were mentioned in the discussion section of Chapter 11. Future studies are needed to further support our claim, or provide evidence against it. Several possible studies would prove helpful in this regard. First, antipsychotic dose is only a crude measure of the activity of these medications on the central nervous system. A large-scale study employing a methodology that directly assays the brain activity of these medications and whether this metric has any relationship to the severity of motivational deficits would provide a stronger form of evidence. We are currently undertaking such an investigation using PET-derived measures of dopamine (D$_2$) receptor blockade and clinical measures of negative symptom burden, including clinical measurements of motivational deficits. Preliminary unpublished analyses have supported our hypothesis that greater antipsychotic-related occupancy of dopamine D$_2$ receptors is not associated with more severe negative symptoms or motivational deficits in particular. More analyses, including those relating to the effect of potentially confounding variables, are needed before this work is complete. Beyond this examination, which includes clinical measures of motivation, studies utilizing performance-based measurements of the discrete components of motivation (e.g., willingness to work for reward) hold promise. It is notable, though, that the invasive nature and cost associated PET studies in schizophrenia preclude a large-scale investigation into antipsychotic-related "side effects." In this regard, a proxy measure of PET-derived antipsychotic-related occupancy may provide an alternative. Dose is a very crude measure, whereas plasma concentration of antipsychotic medications may represent a variable that is more closely linked to the actual brain activity of these medications (508). We have also undertaken a preliminary investigation using a large sample of patients with schizophrenia (including several hundred patients) and examining
whether a relationship exists between plasma levels of antipsychotic medications and severity of motivational deficits. Again, no systematic relationship was found in our preliminary analyses, further providing support for our notion that antipsychotic medications may not necessarily worsen motivation in patients with schizophrenia.

Our work on the relationship between antipsychotic medications, including the work presented in this thesis (study 9) as well as the preliminary analyses described above, challenge the notion that antipsychotics dampen motivation or goal-directed behaviour. This is at odds with decades of work conducted with experimental animals, where single doses of antipsychotics have been found to cause reductions in effortful goal-directed behaviour (493). However, these pre-clinical studies have generally employed single acute-dosing paradigms, a design which does not reflect the conditions under which patients with schizophrenia receive antipsychotic medications. A pre-clinical study employing a chronic-dosing paradigm is needed in order to resolve this question. Before mentioning the specifics of a possible experiment that could provide a more controlled form of evidence for our hypothesis, it should be noted that "normal" wild-type rats do not mirror the conditions of schizophrenia. It is unclear whether antipsychotics (administered chronically) would have differential effects depending of the nature of pathology. In other words, it is unclear whether antipsychotics will have the same behavioural and neurobiological (long-term) effects on healthy controls as they would in patients with schizophrenia. Keeping this point in mind, an experiment in otherwise healthy rats would provide a starting point about how to conceptualize this issue in the context of animal research, and may provide important information of how to design subsequent experiments.

An example experiment could employ either a progressive ratio or an effort-based decision making paradigm as a behavioural measure of incentive motivation, though our preference would be the latter (see Chapter 1 for a discussion). Two sets of rats could be used, where one group received injections of an antipsychotic in depot formulation (e.g., haloperidol decanoate or, alternatively, the drug could be administered via minipump), and the other groups would receive vehicle injections. The frequency of injections would have to be tailored to the half-life of these drugs in animals (1357). Testing could occur at baseline (pre-administration of drug) and again after a few days to examine acute effects of drug administration, and then again after a few weeks to examine whether longer-term chronic administration of antipsychotic drugs effects goal-directed behaviour, and if so, whether this contrasts to their acute effects. The results we
hypothesize from such an experiment are illustrated in Figure 12-1; antipsychotic-treated animals would initially demonstrate reductions in effortful goal-directed behaviour (i.e., reductions in the selection of high effort/high reward options, and bias toward the low effort/low reward option in the context of a effort-based decision making paradigm), but after repeated treatments the animals would habituate to the effects of the medications, and their effort performance would gradually return to basal levels (or close to basal levels).

Figure 12-1. Graph of the hypothesized effect of antipsychotic medications on effortful goal-directed behaviour

Beyond pre-clinical investigations, and returning to studies examining antipsychotic-related occupancy as a proximal measure of these drugs' brain effects, a controlled study in both healthy human participants and patients with schizophrenia would be helpful in teasing apart the effects of these medications on motivation, and at the same time exploring potential differences in behaviours across groups. A study employing subchronic (e.g., 30 days) fixed dosing using multiple doses would provide valuable insights to the question of whether antipsychotics produce
dose-dependent decrements in goal-directed behaviour. In the context of this proposed experiment, the effect of dose, time, and group status could be examined, as well as potential interactions. It would also be critical to use a single antipsychotic type, and measure plasma levels of the drug, if of course PET-derived measurement is not possible.

12.6 Conclusions

The series of studies presented in this thesis advance our understanding of motivational deficits in schizophrenia. The studies demonstrate the importance of these symptoms in terms of their predictive value for functional outcome, as well as their prevalence and persistence over time. The results of the included studies also offer novel evidence for a candidate computational mechanism underlying these deficits, specifically that effort cost computations or the integration of this signal with subsequent processes contributes to the behavioural manifestation of amotivation in schizophrenia. Studies included in this thesis also provide evidence for a robust relationship between motivational deficits and cognition, two domains of schizophrenia psychopathology that are often assumed to be independent. Last, but certainly not least, the final study included in this thesis advanced the notion that chronic dopaminergic blockade by way of antipsychotic medications does not necessarily worsen the severity of motivational deficits in schizophrenia. Taken together, these studies highlight the importance of motivation in schizophrenia, and provide several novel findings about the nature of this domain of illness.
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