UNDERSTANDING TREATMENT-RESISTANT DEPRESSION:
THE COMPLICATED RELATIONSHIPS AMONG NEUROCOGNITION, SYMPTOMS, AND FUNCTIONING

By

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Abstract

**Background:** Treatment-resistant depression (TRD) encompasses a segment of individuals with major depressive disorder who are severely ill in terms of chronicity, comorbidity, and prognosis. Although functional impairment is a prominent and costly feature of treatment-resistance, very little is known about the factors that contribute to and maintain functional impairment in TRD.

**Purpose:** This study examined the relationships among neurocognition, symptoms, and functional impairment in TRD. Specifically, I examined the neurocognitive impairments that relate to different symptom domains and to level of symptom severity, as well as the predictors of functional outcomes and real-world behaviour in TRD.

**Method:** Patients \((N = 29)\) with a diagnosis of major depressive disorder were recruited from the Mood Disorders Treatment and Research Service at Providence Care Mental Health Services in Kingston, Ontario. Data were collected during a baseline assessment for a neurocognitive enhancement therapy program.

**Results:** Individuals with TRD show mild to moderate impairments across all neurocognitive domains, with a superimposed severe impairment in verbal working memory. Verbal working memory significantly correlated with depressive symptoms and anxiety, such that increased verbal working memory capacity was related to more severe clinical symptoms. Greater response inhibition significantly correlated with less anxiety. Interpersonal competence was predicted by sustained attention and severity of depressive symptoms. Adaptive competence was significantly predicted by age at baseline and set shifting. Real-world work behaviour, interpersonal relations, and general
satisfaction were predicted by the severity of depressive symptoms, whereas observed mood and anxiety predicted real-world recreational activity.

Conclusions: The current study pioneered some of the first data regarding the relationships among neurocognition, symptoms, and functional outcomes in treatment-resistant depression. Verbal working memory appears to play an important role in the symptomatology of TRD. Neurocognitive variables and depressive symptoms are important in predicting functional competence (what one can do) but only depressive symptoms predict functional performance (what one actually does in the real world). There may be additional intrinsic or extrinsic factors that mediate the relationships among neurocognition, symptoms, and functioning in TRD.
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Chapter 1

Introduction

Major Depressive Disorder

Major depressive disorder (MDD) is a mental disorder characterized by feelings of sadness or emptiness and diminished interest or pleasure in activities. These symptoms are accompanied by weight loss or weight gain, disturbances in sleep, loss of energy, mental slowing or loss of concentration, feelings of worthlessness, inappropriate guilt, and recurrent thoughts of death and suicide (DSM-IV-TR).

In 2000, the World Health Organization determined that depression was the fourth leading cause of disease burden worldwide and projected that by 2020 it would be the leading cause of disease burden in developed countries. A nationally representative community mental health survey conducted by Statistics Canada revealed that depression affects 12.2% of Canadians over their lifetime, and 4.8% of Canadians annually (Patten et al., 2006). As expected, this epidemiological study found that MDD was more common in women than in men, however, this difference decreased with advancing age. In a national mental health survey conducted in the United States, 72.1% of respondents with MDD also met criteria for at least one other DSM-IV disorder, including 59% with an anxiety disorder, 24% with a substance use disorder, and 30% with an impulse control disorder (Kessler et al., 2003). Canadians who suffer from depression are at increased risk of mortality, due to cardiovascular disease and unnatural causes such as suicide (Wulsin, Vaillant, & Wells, 1999).

Given the prevalence of major depressive disorder and its relationship to other mental and physical health problems, it is not surprising that MDD causes significant cost...
and burden on society. Simon (2003) stated that the three primary areas of social and economic burden associated with MDD are: reduced functional status or quality of life, increased disability expressed as time missed from work or other occupational roles, and the increased cost of health service. Specifically, depression was the third leading cause of loss of quality life, ranking just below arthritis and heart disease (Unutzer et al., 2000) and was associated with a 2.5-fold increase in missing work due to illness and a 50% increase in time lost from work (Kessler et al., 1999). Furthermore, depressive disorders are associated with a 50%-75% increase in overall health service costs even after adjusting for comorbid chronic medical conditions. However, a recent and encouraging review of randomized control trials and longitudinal studies demonstrated that improvement in depression was associated with increased quality of life, increased work productivity, and reductions in costs of general medical services (Simon, 2003).

Symptom Domains and Course of Illness

The symptoms of MDD can be quite heterogeneous, however, a recent factor analytic study by Uher et al., (2007) suggested three distinct symptom domains of the disorder. Merging items from three well-established assessment measures, the Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960), the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) and the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown 1996), the factor analysis yielded three symptom domains: observed mood and anxiety, cognitive, and neurovegetative. The observed mood and anxiety factor consisted of clinician-rated anxiety, mood, and activity items. The cognitive factor included items of suicide, guilt, pessimism, and self-
deprecation. The *neurovegetative* factor consisted of items related to appetite, weight loss, sleep, and sexual drive.

In addition to its varying symptomatology, the course of MDD is also variable. According to the American Psychological Association, some individuals may have isolated depressive episodes that are separated by years of euthymia, whereas others may have depressive episodes that increase in frequency and severity over time. After one year of a diagnosis of MDD, 40% of individuals still meet criteria for the disorder.

Treatment-Resistant Depression

Treatment-resistant depression (TRD) encompasses a segment of individuals with major depressive disorder who are severely ill in terms of chronicity, comorbidity, and prognosis (Kornstein & Schneider, 2001). The current criterion for TRD is a failure to achieve remission of clinical symptoms following at least one trial of an antidepressant medication at an appropriate dose and duration (Thase and Rush, 1997; Fava, 2003). Varying degrees of resistance have been proposed, ranging from the aforementioned criterion (Stage I) to response failures in three other classes of treatment plus bilateral electroconvulsive therapy (Stage V; Thase and Rush, 1997). Although TRD has been defined with several different sets of criteria, all definitions are centered on the fact that these patients experience chronic depression for years on end. In addition to the persistence of clinical symptoms, treatment resistance is associated with severe and pervasive impairments in areas of psychosocial functioning. In a study by Petersen et al., (2004), clinicians used a scale of psychosocial functioning called the Longitudinal Interval Follow-up Evaluation (LIFE), in which ratings ranging from ‘very poor’ to ‘very good’ were made on a variety of life domains. Clinicians rated this sample of patients
with TRD as experiencing mild to moderate impairment in work-related activities, good
to fair interpersonal relationships, poor level of involvement in recreational activities, and
mild impairment in their enjoyment of sexual activity. Both patients and clinicians rated
global social adjustment as poor. Therefore, treatment-resistant depression is associated
with severe and pervasive impairments in many areas of psychosocial functioning,
including occupation, interpersonal relations, and recreation. However, very little, if any,
information exists on the factors that contribute to the functional impairments observed in
TRD. It is likely that multiple factors unique to treatment-resistance, such as the
magnitude of neurocognitive impairment, severity of depressive symptoms, and
chronicity of the illness are related to functioning, however the exact nature of these
relationships remains unclear.

Is Functional Recovery Attainable?

Functional impairment is a complex and poorly understood feature of treatment-
resistant depression. Although not much is known about functional recovery in TRD,
there is a considerable amount of literature on functional recovery in MDD. Individuals
with MDD may experience impairment in a variety of life domains, including
interpersonal relationships, academic or occupational achievement, independent living,
and community participation. In fact, depression is the primary source of disability in the
Canadian workplace (Dewa, Lesage, Goering, & Craveen, 2004). Perhaps surprisingly,
the mood symptoms associated with MDD do not fully account for the breadth and
persistence of functional impairment experienced by individuals with this disorder. Only
20% of patients achieve full functional recovery, whereas another 20% remain
permanently debilitated (Andrews, 2001; Judd et al., 1998). Although functional
impairment is a prominent and costly feature of MDD, very little is known about the factors that contribute to and maintain functional impairment in major depressive disorder, let alone treatment-resistant depression.

Standard pharmacological and psychological treatments target mood symptoms, however amelioration of mood symptoms is not always associated with functional recovery. In other psychiatric populations, many patients experience residual impairment in social and occupational functioning despite psychopharmacological intervention (Gold et al., 2002; Green & Nuechterlein, 1999; Velligan et al., 1997). One of the most prominent predictors of functional outcomes in other psychiatric disorders, such as schizophrenia and bipolar disorder, is neurocognitive functioning (Bowie et al., 2008; 2010). In a study of neurocognitive function and disability in MDD, baseline neurocognitive performance predicted level of functioning six months later, even after controlling for depressive symptoms (Jaeger et al., 2006). Individuals with MDD whose neurocognitive function declined over a six-month period remained significantly disabled. Greater magnitude of neurocognitive deficits may be associated with a more severe and debilitating form of the illness and more frequent hospitalizations (Jaeger et al., 2006). Although there has been some evidence to suggest that neurocognitive changes in depression are associated with functional outcomes, few studies have examined this relationship, and the role of neurocognition in functional recovery in MDD, let alone TRD, remains poorly understood. Since mood symptoms do not fully account for the breadth of impairment experienced in this disorder, the association between neurocognition and functional impairment in TRD is an area in need of investigation.
The Profile of Neurocognitive Impairments in MDD

The neurocognitive profile of TRD is unknown. However, in major depressive disorder, neurocognitive deficits are evident across multiple domains, including attention (Schatzberg et al., 2000; Dunkin et al., 2000; Landro et al., 2001), memory (Purcell et al., 1997; Basso & Bornstein, 1999), visuospatial processing (Coello et al., 1990; Henriques & Davidson, 1997; Bulbena & Berrios, 1993; Porter et al., 2003), verbal and non-verbal learning (Basso & Bornstein, 1999), motor functioning (Landro et al., 2001; Borkowska & Rybakowski, 2001; Swann et al., 1999) and executive functioning (Merriam et al., 1999; Schatzberg et al., 2000; Trichard et al., 1995; Paradiso et al., 1997). These deficits are specific to severe mental illnesses such as MDD and are not a function of general disease-related factors, (e.g., stress or not feeling well). A study by Den Hartog et al., (2003) compared neurocognitive functioning in healthy controls, patients with chronic allergic rhinitis, and patients with MDD. Only the individuals with MDD exhibited impairment in neurocognitive performance. The authors concluded that the deficits seen in depression could not be ascribed to more general physical disease-related factors (e.g., stress, not feeling well) as these experiences are also present in patients with severe chronic allergic rhinitis. Therefore, the neurocognitive impairments in MDD are likely related to an inherent neurological component of the illness and are not simply due to having a chronic illness.

Two hypotheses have been proposed to account for the neurocognitive deficits observed in MDD. One hypothesis, the effort hypothesis, states that individuals with depression have difficulty with effortful cognitive tasks that require elaborate processing, such as memory rehearsal, executive functioning, working memory, and systematic
searching. The other hypothesis, the cognitive speed hypothesis, states that depression is characterized by a cognitive slowing, which becomes the source of general cognitive dysfunction. According to this hypothesis, cognitive slowness, or reduced information processing, is responsible for deficits in higher-order cognitive processes. The literature in this field is mixed and there is research in support of both hypotheses. Den Hartog et al., (2003) found that depressive patients differed from controls on automatic cognitive tasks (such as word reading and memory span) but not on tasks that required more effortful processing (such as concept shifting, response inhibition, and controlled search), lending support to the cognitive speed hypothesis. However, other researchers support the effort hypothesis and have found that individuals with depression do differ from controls on tasks that require effortful processing, such as executive functioning (Grant et al., 2001; Purcell et al., 1997). The true mechanism of neurocognitive impairment in MDD remains equivocal.

The Importance of Neurocognition

There is a growing body of literature examining core characteristics of depression, such as rumination, and their association with deficits in working memory and executive function. Recent research suggests that difficulty updating the contents of working memory and difficulty removing irrelevant negative material from working memory is associated with depressive symptoms (Joorman & Gotlib, 2008). In addition, research with healthy controls demonstrated that impairment in task shifting or inhibitory control is compounded as working memory load increases (Hester & Garavan, 2005), which may be implicated in the maladaptive thought patterns often seen in depression. Literature bases from clinical psychology and the fields of cognition and memory are just starting to
come together to examine the role of executive function and working memory in MDD. The implications of executive function and working memory in the maintenance of the rumination cycle are still unclear. Given the chronic nature of treatment-resistant depression, it is likely that the literature surrounding neurocognitive function in other severe and chronic mental disorders, such as schizophrenia and bipolar disorder, may provide a basis for conceptualizing the role of neurocognition in determining functional outcomes in TRD.

While some research has suggested that individuals with MDD are less cognitively impaired than people with schizophrenia, other studies (e.g., Albus et al., 1996; Sweeny et al., 2000) have found little difference in neurocognitive performance between individuals with MDD and those with schizophrenia or bipolar disorder. In the case of MDD, the presence of psychotic symptoms has been associated with more severe neurocognitive impairments (Burdick et al., 2006). In addition, the magnitude and scope of neurocognitive deficits are typically more severe in treatment-resistant depression than in patients who are responsive to treatment (Harvey, 2007). Treatment-resistant depression is also associated with cortical atrophy (Shah et al., 2002), which may have important implications for neurocognitive function. To my knowledge, there is no data examining the relationship between cortical atrophy and neurocognitive function in treatment-resistant depression. However, there is evidence from the dementia literature to suggest a relationship between cortical atrophy and neurocognitive impairment. Cerebral white matter lesions have been associated with impairments in psychomotor speed and global neurocognitive function in senior adults, both with and without dementia (de Groot et al., 2000). Severity of global neurocognitive impairment (assessed
using the Mini-Mental State Examination and Clinical Dementia Rating scale) significantly correlated with hippocampal and cortical gray matter atrophy (Fein et al., 2000). In fact hippocampal atrophy was the best predictor of severity of neurocognitive impairment. Surprisingly, very little research has examined the neurocognitive characteristics of treatment-resistant depression.

In other psychiatric populations, neurocognitive impairment has been linked to various demographic, clinical, and course of illness variables, in addition to functional outcomes (Bowie et al., 2008; 2010). Previous work with schizophrenia and bipolar disorder suggests that there are complex direct and indirect relationships between neurocognitive ability and functional outcomes. Certain neurocognitive domains are important for the acquisition of interpersonal or adaptive skills, while others may be important for the deployment of these skills in the real world. For example, previous research in schizophrenia (e.g., Bowie et al., 2008; 2010) has shown that verbal memory and executive functioning are important for the acquisition of adaptive competence, but are less predictive of the development of social skills. However, other neurocognitive domains, such as processing speed, attention, and working memory are associated with both adaptive and social competence. Interestingly, performance in processing speed directly predicted real-world work, interpersonal, and community behaviour, whereas performance across other neurocognitive domains, including attention, working memory, and executive functioning, indirectly predicted these real-world behaviours, such that the relationship between neurocognition and real-world behaviour was mediated by the individual’s level of adaptive and social competence (Bowie et al., 2008; 2010).
The literature on neurocognitive deficits in psychiatric illness has largely focused on brain injury and schizophrenia-spectrum conditions, however, there are several reasons to believe that neurocognition may be equally relevant to functioning in MDD, particularly TRD. First, there are overlapping clinical and neurocognitive dimensions across the schizophrenia and affective disorder spectrums. Second, although the magnitude of impairment is less, the profile of neurocognitive impairment in affective disorders is similar to that seen in schizophrenia. Third, although findings from genetic risk studies remain heated and controversial, there is some evidence to suggest that the neurocognitive impairments observed in schizophrenia and affective disorders share etiological mechanisms (Hill et al., 2008) and underlying neurophysiology (Bearden et al., 2001). To date, no study has examined the complexity of the relationships among clinical variables, neurocognition, and functioning in treatment-resistant depression.

The Current Study

Limited research has been conducted on the neurocognitive characteristics of treatment-resistant depression. To date, there are no published data examining the relationship among neurocognition, symptoms, and functional outcomes in TRD. The purpose of this study is to examine the relationships among symptoms, course of illness, neurocognition, and functional impairment in treatment-resistant MDD. Specifically, I will investigate the neurocognitive impairments that relate to different symptom domains and to level of symptom severity, as well as examine the predictors of functional outcomes and real-world behaviour in TRD.

Importantly, this will be the first study to use objective, performance-based measures of interpersonal and adaptive functioning (in addition to self-report or clinician-
rated measures) to assess functional impairment in TRD. Performance-based measures use props or role-play to assess an individual’s capabilities or competence in the laboratory. Performance-based measures of functioning assess what an individual can do (competence) and not what he or she actually does in the real world. Performance-based measures of competence provide an advantage because they are not confounded by external constraints such as restricted housing situations, limited social contact, low income, and stigma. In the current study, I will use a combination of performance-based measures and third-party ratings of real-world behaviour to assess functioning in order to capture the individual’s competence (what he or she can do in the laboratory) and performance (what he or she actually does in the real world).

There are three objectives for this study:

(1) Determine the relationship between neurocognition and symptom severity in treatment-resistant depression.

(2) Explore the differential relationships between neurocognitive domains (e.g., processing speed, working memory, executive function) and symptom domains (i.e., observed mood and anxiety, cognitions/maladaptive thought patterns, and neurovegetative symptoms) in treatment-resistant depression.

(3) Determine the predictors of functional competence and performance in TRD using both objective performance-based measures of competence and measures of real-world behaviour.

Hypotheses

In order of the aforementioned objectives, I hypothesize that (1) based on previous research linking the severity of neurocognitive impairment with more
debilitating illness and more frequent hospitalizations, there will be a positive linear relationship between neurocognitive impairment and severity of depressive symptoms; (2) the symptom domains of observed mood and maladaptive thought patterns will be related to executive functioning and verbal working memory. This hypothesis is based on a growing body of literature on depressive symptoms and rumination and their association with difficulty updating the contents of working memory and impaired task shifting as working memory load increases. I also hypothesize that neurovegetative symptoms will be related to problems with sustained attention and slowed processing speed, due to the face validity of these relationships; (3) similar to other psychiatric conditions, neurocognition will emerge as a prominent predictor of functional impairment in TRD, even with the contribution of demographic information, mood symptoms, and course of illness variables.
Chapter 2

Method

Participants

Patients (N = 29) with a diagnosis of major depressive disorder were recruited from the Mood Disorders Treatment and Research Service at Providence Care Mental Health Services in Kingston, Ontario. Participants recruited for this study had evidence of at least Stage 1 treatment resistance according to the Thase and Rush (1997) definition, described previously. The inclusion criteria were men and women with a diagnosis of Major Depressive Disorder, age 18-65, currently engaged in outpatient treatment. Exclusion criteria included a medical diagnosis associated with neurocognitive impairment (e.g., dementia, cerebrovascular accident, traumatic brain injury), and a reading level below Grade 6 as assessed with the Wide Range Achievement Test-Reading Recognition subtest (WRAT3; Wilkinson, 1993) because of the likelihood of not understanding instructions, and uncorrectable hearing or visual impairments that would preclude assessment procedures.

Measures

The following measures were obtained at baseline of a 10-week neurocognitive enhancement therapy program.

Neurocognition

The neurocognitive battery employed in this study consisted of a selection of standardized tests that are frequently used in both research and clinical settings. The tests were selected based on neurocognitive domains known to be impaired in depression. All tests were user-friendly, provided minimal burden on participants, and had strong
psychometric properties. The entire battery took approximately 45 minutes. Raw data were converted to gender-corrected, age-corrected, and/or education-corrected standard scores based on normative data from healthy control subjects, which were found in the test administration manuals or in the Spreen & Strauss (1998) compendium of neuropsychological tests. A neurocognitive composite score was computed by calculating an equally weighted average from the following domains:

**Sustained Attention** refers to maintaining focus on a set of stimuli, while ignoring irrelevant stimuli. Sustained attention was assessed using the *Continuous Performance Test – Identical Pairs Version* (CPT-IP; Cornblatt et al., 1988). The CPT-IP is a computerized measure of sustained attention that involves monitoring a series of digits as they are presented for 500ms on a computer screen and responding with a button press each time that two stimuli in a row are identical. The dependent variable was the mean $d'$ value across 2-, 3- and 4-digit conditions. The $d'$ is a statistic used in signal detection theory. This theory assumes that noise is normally distributed in the environment. Presenting a signal on top of that noise shifts the amount of sensory activity. The difference between the mean amount of sensory activity generated by the ‘noise alone’ trials and the ‘signal plus noise’ trials will equal $d'$, which is measured as a $z$-score (Heeger, 2007). In other words, $d'$ is an index of signal/noise discrimination that is computed by the CPT-IP program. The formula for $d' = z(\text{hit rate}) - z(\text{false alarm rate})$. A higher $d'$ indicated that the signal was more readily detected. The CPT-IP was standardized on a sample of 300 healthy adults aged 20 to 59 as part of the National Institute of Mental Health (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery (Nuechterlein &
Green, 2006). According to the MATRICS manual, the test-retest reliability coefficient \((r)\) over a four-week period in individuals with schizophrenia was .74 with an intraclass correlation (ICC) of .74.

**Verbal Learning** refers to learning new information, such as a list of words over a series of trials. The *Hopkins Verbal Learning Test* (HVLT-R; Brandt & Benedict, 2001) is a list-learning task of verbal declarative memory in which participants are presented with 12-word lists over 3 learning trials. The dependent variable was the number of words correctly recalled by the respondent over the three trials. Therefore, the total recall raw score is summed across all three trials of the word lists. The HVLT-R was standardized on a sample of healthy adults \((N = 300)\) aged 20 to 59 as part of the NIMH MATRICS consensus cognitive battery. The test re-test reliability was reported as .69 with an ICC of .68 (Nuechterlein & Green, 2006).

**Verbal Working Memory** refers to the capacity to simultaneously store and manipulate information. The *Letter Number Sequencing Test* (LNS; Gold et al., 1997) is an auditory working memory test, where participants were require to listen to presentations of numbers and letters and to mentally reorder (numbers in ascending order, followed by the letters in alphabetical order) the presented lists of intermixed letters and numbers before repeating them back to the test administrator. Thus, this verbal working memory task engaged both the maintenance and manipulation components of working memory. The dependent variable was the number of correct responses. The total score was the sum of the individual scores for each trial. The LNS test was standardized on a sample of 300 healthy adults aged 20 to 59 as part of the NIMH MATRICS consensus
cognitive battery. The test re-test reliability was .81 with an ICC of .78 (Nuechterlein & Green, 2006).

**Information Processing Speed** refers to the ability to quickly and accurately respond to stimuli in the environment. Information processing speed was assessed using the *Digit Symbol Substitution Task* (Keefe, 1999) and *Trail Making Test Part A* (TMT-A; Partington & Leiter, 1949).

The Digit Symbol Task is a measure of processing speed that involved writing numbers that correspond to symbols as quickly as possible for a 90-second period. Although the ability to remember the paired symbols and numbers plays a role in performance, processing speed is the primary determinant of performance. The dependent variable was the total number of correct responses. The Digit Symbol Task was standardized on a sample of healthy adults (N = 300) aged 20 to 59 as part of the NIMH MATRICS consensus cognitive battery. The test re-test reliability coefficient and ICC were .85 (Nuechterlein & Green, 2006). The inter-rater reliability for Part A was .94 (Spreen & Strauss, 1997).

The *Trail Making Test Part A* involved using a pencil to connect 25 consecutive numbers that are arranged in irregular locations on a sheet of paper. Unlike Part B (described below), Part A does not involve switching between two sets of consecutive stimuli and, therefore, does not emphasize working memory and set shifting. The dependent variable was time to completion, in seconds. The TMT-A was standardized on a sample of healthy adults (N = 300) aged 20 to 59 as part of the NIMH MATRICS consensus cognitive battery. The test re-test reliability coefficient was reported as .77 with an ICC of .75 (Nuechterlein & Green, 2006).
The reliability of the Digit Symbol Task and the Trail Making Test Part A in comprising the information processing speed domain was adequate (Cronbach’s alpha = .57).

**Verbal Fluency** refers to the ability to access words efficiently. Verbal fluency was assessed using the *Controlled Oral Word Association Test* (COWAT) and *Animal Naming* tests (Spreen & Benton, 1969; 1977). These tests were used to measure letter fluency and category fluency, respectively. The purpose of the tests was to evaluate the spontaneous production of words beginning with a given letter or of a given category within a limited amount of time. The COWAT involved orally producing as many words as possible beginning with a given letter in 60 seconds. The letters F, A, and S are the most commonly used letters and were therefore used in the current study. The dependent variable was the number of correct words named in 60 seconds. The COWAT was standardized on a sample of healthy adults (N = 894) aged 16 to 95 years (Tombaugh, Kozak, & Rees, 1996). Inter-scorer reliability for one-year retest reliability in older adults has been reported as .70, that is .70 for the letter F, .60 for the letter A, and .71 for the letter S (Snow et al., 1988).

The Animal Naming test is a category fluency task that evaluates the spontaneous production of words. It involved asking participants to name as many animals as possible within 60 seconds. The dependent variable was the number of correctly identified animals in 60 seconds. The Animal Naming test was standardized on a sample of 300 healthy adults aged 20 to 59 as part of the NIMH MATRICS consensus cognitive battery. The test re-test reliability coefficient and ICC were .74 (Nuechterlein & Green, 2006).
The reliability of the COWAT and Animal Naming tests in comprising the verbal fluency domain was acceptable (Cronbach’s alpha = .63).

Executive Functioning refers to the ability to plan ahead, solve problems, engage in abstract thinking, and coordinate other cognitive skills. Executive functioning was assessed as two separate components. Response inhibition was assessed using the Stroop Color-Word Test (Golden, 1978) and set shifting was assessed using the Trail Making Test Part B (TMT-B; Partington & Leiter, 1949).

Response inhibition and set shifting tests were separated into different variables because combining the two tests to create an executive functioning domain yielded an unacceptable low reliability (Cronbach’s alpha = .23). A scatterplot of the two variables revealed that there was one extreme outlier (z-score < -6), on the Trail Making Test Part B. However, even after removing this case from the reliability analysis, the reliability of the executive functioning domain was still very low (Cronbach’s alpha = .25). Therefore, response inhibition and set shifting were examined as separate neurocognitive domains.

Response Inhibition. The Stroop Test is a measure of attention, response inhibition, and cognitive flexibility. It measures the ease with which a person can shift his or her perceptual set to conform to changing demands and their ability to focus on a salient feature of stimuli while simultaneously inhibiting response to a distracting feature of the same stimuli. In other words, it assesses the ability to suppress a habitual response in favour of an unusual one. There are several versions of the Stroop test. The version used in the current study has three parts, each using a white card with stimuli presented in rows. In Part 1 (Word Score), the participant read randomized colour names (blue, green, red, yellow) printed in black type. In Part 2 (Colour Score), the participant had to name
the ink colour of four typed Xs, (i.e., XXXX). In Part 3 (Colour-Word Score), the participant read the colour of the print, ignoring the colour names printed in coloured ink (the print never corresponded to the colour name). This measure was used primarily to assess the colour-word interference effect, which is when the participant has to inhibit their usual response in order to read the coloured words printed in non-matching coloured ink. The dependent variable represented the colour-word interference effect, which was calculated as a difference score that subtracts the Stroop predicted colour-word performance score from the observed Stroop Colour Word Score. The predicted score was calculated as follows: (Word Score x Colour Score) / (Word Score + Colour Score).

The Stroop test was standardized on a sample of 188 healthy adults with above-average educational achievement (Spreen & Strauss, 1997). Previous reports of the test-retest reliabilities for the average of three trials were above .75. A report of test-retest reliability using a one-month interval between sessions had reliability coefficients of .90, .83, and .91 for the three parts of the test (Spreen & Strauss, 1997).

Set Shifting. The Trail Making Test Part B required the participant to alternate their attention between two salient features of a stimulus. It involved using a pencil to connect 25 encircled numbers and letters in alternating order. Unlike Part A of the Trail Making Test, it emphasized working memory and set shifting. Part A and Part B correlated with each other at $r = .49$, suggesting that they do measure somewhat different functions (Heilbronner et al., 1991). The dependent variable was the time to completion, in seconds. The TMT-B was standardized on a sample of 308 healthy adults aged 20 to 85 (Invik, Malec, & Smith, 1996). The inter-rater reliability for Part B was reported as .90 (Spreen & Strauss, 1997).
The **Neurocognitive Composite Score (NCS)** was an equally weighted average of all of the neurocognitive domains. It was calculated by converting each of the dependent variables described above into z-scores. The information processing speed and verbal fluency domains consisted of more than one neurocognitive measure; therefore the z-scores for the dependent variables within these two domains were averaged to create the domain scores. Finally, the z-scores from all of the neurocognitive domains were averaged to create NCS. The computation for the NCS has consistently been used in other research (e.g., Keefe et al., 1999; Nuechterlein & Green, 2006). The reliability of the NCS in the current sample was .74.

Domain formulas:

- **Sustained Attention** = MEAN (CPT d’ 2-DIGITS, d’ 3-DIGITS, d’ 4-DIGITS).
- **Verbal Learning** = SUM (HVLT Trial 1, Trial 2, Trial 3).
- **Verbal Working Memory** = Letter Number Sequencing.
- **Information Processing Speed** = MEAN (Symbol Coding, Trail Making Test A).
- **Verbal Fluency** = MEAN [COWAT (Letters F, A, S), Animal Naming)].
- **Response Inhibition** = Stroop Test
- **Set Shifting** = Trail Making Test B.

Neurocognitive Composite Score formula:

\[ NCS = \text{MEAN (Sustained Attention, Verbal Learning, Verbal Working Memory, Information Processing Speed, Verbal Fluency, Response Inhibition, Set Shifting).} \]
I collected measures of depressive symptoms and anxiety. The 17-item Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) is a semi-structured interview used to measure the severity of depressive symptoms in the past week. The HAMD takes approximately 20 minutes to administer. The HAMD item ratings range from 0 to 2 or from 0 to 4 based on severity, with a total score from 0 to 50 for the 17 items. Higher scores indicated more severe depressive symptoms. The internal consistency of the HAMD in a study of 141 participants was .76 (Rehm & O’Hara, 1985) and .92 in a study of more than 300 participants (Reynolds & Kobak, 1995). The internal consistency reliability coefficient for the HAMD in the current sample was .75.

The 10-item Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) is also a semi-structured interview that was used as a measure of depressive symptom severity. The items scales range from 0 to 6, and half-point scoring is allowed. The total score ranges from 0 to 60, with higher scores indicating more severe depressive symptoms. The MADRS took approximately 15 minutes to administer. The reliability of the MADRS was acceptable and comparable to the reliability of other clinician rated depressions scales. Correlations between each item and the remaining items ranged from .12 (reduced appetite) to .84 (apparent sadness) and joint reliability for the total score in several studies ranged from 0.76 to 0.95 (Davidson et al., 1986; Montgomery and Asberg, 1979). In one study, change scores on the MADRS and the HAMD were compared with global expert ratings (Montgomery and Asberg, 1979). The MADRS had a correlation of .70 with the change in global expert ratings, whereas the HAMD had a correlation of .59 with the change in global expert ratings, suggesting that
the MADRS may be sensitive to changes in the severity of depressive symptoms. The internal consistency coefficient of the MADRS in the current sample was .73.

Three distinct depressive symptom domains were created based on the proposed model of symptom dimensions by Uher et al., (2007). The specific items from the MADRS and HAMD outlined by Uher et al., (2007) were combined to create the following three factors: observed mood, cognitive, and neurovegetative (see Table 1). The reliabilities for observed mood, cognitive, and neurovegetative in the current sample were .80, .76, and .58, respectively. The correlations among the three factors were equal to or less than .65, so there was no problem of multicollinearity. For the purposes of this study, the cognitive factor will now be referred to as maladaptive thought patterns in order to avoid confusion with neurocognitive variables.

Table 1. Exploratory factor analysis: three-factor solution with PROMAX rotated loadings (Uher et al., 2007)

<table>
<thead>
<tr>
<th>Observed Mood</th>
<th>Maladaptive Thought Patterns</th>
<th>Neurovegetative Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS 1</td>
<td>Mood observed</td>
<td>MADRS 9 Pessimism</td>
</tr>
<tr>
<td>MADRS 2</td>
<td>Mood reported</td>
<td>MADRS 10 Suicide</td>
</tr>
<tr>
<td>MADRS 3</td>
<td>Tension</td>
<td>HAMD 2 Guilt</td>
</tr>
<tr>
<td>MADRS 6</td>
<td>Concentration</td>
<td>HAMD 3 Suicide</td>
</tr>
<tr>
<td>MADRS 7</td>
<td>Lassitude</td>
<td>HAMD 6 Sleep, late</td>
</tr>
<tr>
<td>MADRS 8</td>
<td>Inability to feel</td>
<td>HAMD 12 Appetite</td>
</tr>
<tr>
<td>HAMD 1</td>
<td>Mood</td>
<td>HAMD 14 Sexual</td>
</tr>
<tr>
<td>HAMD 7</td>
<td>Activity</td>
<td>HAMD 17 Weight loss</td>
</tr>
<tr>
<td>HAMD 8</td>
<td>Retardation</td>
<td></td>
</tr>
<tr>
<td>HAMD 9</td>
<td>Agitation</td>
<td></td>
</tr>
<tr>
<td>HAMD 10</td>
<td>Anxiety, psychic</td>
<td></td>
</tr>
<tr>
<td>HAMD 11</td>
<td>Anxiety, somatic</td>
<td></td>
</tr>
<tr>
<td>HAMD 13</td>
<td>Somatic symptoms</td>
<td></td>
</tr>
<tr>
<td>HAMD 15</td>
<td>Hypochondrasis</td>
<td></td>
</tr>
</tbody>
</table>

Note. Item HAMD-16 (Loss of Insight) is omitted from the factor analysis because it did not load onto any of the factors; additionally, in the current study sample, there was zero variance for item HAMD-16, as each and every participant scored a zero – in other words, they were all aware that they had a psychological disorder.
The Beck Anxiety Inventory (BAI; Beck et al., 1988) is a 21-item self-report instrument that was used to assess somatic, subjective, and panic-related symptoms. The BAI employs a 4-point Likert scale ranging from 0 (not at all) to 3 (severely: I could barely stand it). The total score ranges from 0 to 63, and the following guidelines were recommended for the interpretation of scores: 0-9 = normal or no anxiety; 10-18 = mild to moderate anxiety; 19-29 = moderate to severe anxiety; and 30-63 = severe anxiety.

The BAI had high internal consistency, .90 to .94, and test-retest reliability correlation coefficients of .67 to .93 over a one-week interval, and .62 over a 7-week interval (BAI; Beck et al., 1988). The internal consistency reliability of the BAI in the current sample was .88.

*Measures of functioning*

Performance-based measures are objective, laboratory-based assessments in which participants are asked to engage in everyday situations through role-play. These measures allow for the assessment of an individual’s capabilities, rather than their performance in the real world. A major issue in the interpretation of functional disability is that factors other than competence can impact real-world performance. Therefore, I also used self-report and behavioural observations rated by a third-party informant as measures of real-world behaviour.

*Performance-based measures of functional competence* ![Image](image.png)

**Interpersonal competence.** The Social Skills Performance Assessment (SSPA: Patterson et al., 2001) is a measure of social competence and communication. After a brief practice session, patients initiated and maintained a conversation for 3 minutes in each of two situations. In Scene 1, the participant was asked to greet a new neighbor and
in Scene 2, the participant was asked to call a landlord to request a repair for a leak that has gone unrepaired. The sessions were audiotaped and scored by a trained rater who was unaware of diagnosis, study purpose or procedures, and all other data, with the exception of the affect and grooming items, which were rated by the administrator in-person. Dimensions of social skills scored in Scene 1 included interest, fluency, clarity, focus, affect, overall conversation, grooming, and social appropriateness. Dimensions of social skills scored in Scene 2 included interest, fluency, clarity, focus, affect, negotiation ability, submissive-persistent, overall argument, grooming, and social appropriateness. Each item was scored on a scale from 0 to 5, for a total score range of 0 – 95. Higher scores indicated better interpersonal competence. Raters were trained to the gold standard ratings proposed by the instrument developers (ICC = .86). The reliability of the items that comprise the SSPA total score in the current sample was .86.

**Adaptive competence.** Adaptive everyday living skills were assessed using the advanced finances task (Heaton et al., 2004). In this task, individuals were asked to pay fictitious bills and manage a checkbook. They were provided with blank checks, a checkbook register, deposit slips, three bills to pay, and a calculator. They were required to pay each bill while managing their checkbook balance. The most difficult part of this task involved asking individuals to pay off as much of their credit card bill as they could while assuring that they keep $100 in their account for other needs. Points were awarded for correctly paying each bill, writing checks, filling out the deposit slip, balancing the register, and making sure that there was a final balance of at least $100. The task took approximately 10 minutes to complete and a maximum of 17 points could be attained. Higher scores indicated better adaptive competence.
Both the SSPA and the advances finances task have been widely used in
neuropsychiatric populations in the past and have high sensitivity to neurocognitive
deficits and indices of real-world functioning (Heaton et al., 2004; Bowie et al., 2010).

Real-world disability

The Range of Impaired Functioning Tool (LIFE-RIFT; Leon et al., 1999) is a 15-
minute semi-structured interview of the patient’s functional performance in four domains:
work, interpersonal relations, global satisfaction, and recreation. Since the LIFE-RIFT
required some clinical judgment on the part of the interviewer, the interviews were
conducted by and rated by trained graduate students enrolled in a clinical psychology
program. The interviewer asked questions guided by the behavioural anchors provided
for each item in order to make the rating (1 = no impairment to 5 = severe impairment).
The LIFE–RIFT scale score was a sum of the maximum values from each domain. Note
that the ‘work ’ and ‘interpersonal relations ’ domains included multiple items. For
example, the interpersonal relations domain included an item score for relationship with
spouse, children, family, and friends. The total score for the domain represented the most
impaired (i.e. maximum) value among multiple items addressing the domain. Higher
scores indicated more severe impairment.

Procedure

Data were collected during a baseline assessment for a 10-week neurocognitive
enhancement therapy program. The assessment measures were administered over one or
two sessions and took approximately 2 to 2.5 hours to complete. Participants were
compensated with $20 for their time. Graduate students enrolled in a clinical psychology
program conducted the symptom assessments. Trained undergraduate students or
bachelor-level laboratory staff administered the neurocognitive battery and functional competence tasks. The order of assessment was not controlled in this study, as some participants received the neurocognitive assessment prior to the symptom assessment and vice versa.

Data Analysis

In order to address my hypothesis that there will be a positive linear relationship between neurocognitive impairment and severity of clinical symptoms, I applied two-tailed bivariate correlations to examine the relationship between the neurocognitive variables and symptom severity as assessed on the MADRS, the HAMD, and the BAI.

I used two-tailed bivariate correlations in order to examine whether impairments in specific neurocognitive domains map onto different symptom domains. The various neurocognitive domains (sustained attention, verbal memory, verbal working memory, verbal fluency, information processing speed, response inhibition, and set shifting) were created based on what is known to be impaired in depression, and have consistently been used in the literature (e.g., Harvey et al., 2004; Jaeger et al., 2006; Naismith et al., 2007). The symptom domains (observed mood, maladaptive cognitive patterns, and neurovegetative symptoms) were based on the factor analytic study conducted by Uher et al (2007). A Dunn-Sidak correction was applied to account for inflated Type I error.

To address the question of whether neurocognition emerges as a prominent predictor of functional impairment in TRD, stepwise regression analyses were used to determine predictors of functional skill impairment and real-world behaviour. Demographic, course of illness, symptom, and neurocognitive variables were entered as
predictors for each functional skill domain (interpersonal and adaptive competence) and clinician rated real-world behaviour (work, interpersonal, satisfaction, recreation).
Chapter 3

Results

Participants

The participant sample was composed of 21 women and 8 men between the ages of 25 and 74 ($M_{age} = 47.3, SD = 11.3$). Participants had an average of 14 years of education and approximately 72% of the sample was unemployed at the time of the assessment. Age of first psychiatric hospitalization ranged from 12 to 56 years ($M = 24.0, SD = 19.9$). Participants were hospitalized 1 to 50 times ($M = 5.0, SD = 12.7$) and spent a total of 0.5 to 54 months in the hospital ($M = 5.7, SD = 13.2$) over their lifetime. The amount of time elapsed since their last hospitalization ranged from 1.5 months to 2 years ($M = 35.7, SD = 58.6$). Please refer to Table 2 for means and standard deviations of all measures. All measures listed in Table 2 had a skewness value below 1.5 and a kurtosis value below 3.0.
Table 2. Means and standard deviations for all neurocognitive and functioning measures

<table>
<thead>
<tr>
<th>Category</th>
<th>Measure</th>
<th>Observed range</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognition</td>
<td>Neurocognition composite&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1.9 to 0.4</td>
<td>-0.83</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Sustained attention&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-2.7 to 1.1</td>
<td>-0.60</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>Verbal learning&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-2.2 to 1.0</td>
<td>-0.79</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Verbal working memory&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-3.0 to 1.1</td>
<td>-1.67</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>Verbal fluency&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-4.7 to 1.9</td>
<td>-0.67</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>Information processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-2.9 to 1.0</td>
<td>-0.74</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Response inhibition&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-2.4 to 1.5</td>
<td>-0.21</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Set-shifting&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-6.4 to 1.0</td>
<td>-0.82</td>
<td>1.72</td>
</tr>
<tr>
<td>Functional competence</td>
<td>Advanced Finances&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 to 17</td>
<td>10.33</td>
<td>5.41</td>
</tr>
<tr>
<td></td>
<td>SSPA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37 to 80</td>
<td>66.45</td>
<td>10.70</td>
</tr>
<tr>
<td>Symptoms</td>
<td>BAI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 to 51</td>
<td>22.31</td>
<td>11.31</td>
</tr>
<tr>
<td></td>
<td>MADRS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 to 39</td>
<td>24.68</td>
<td>8.18</td>
</tr>
<tr>
<td></td>
<td>HAM&lt;sup&gt;b&lt;/sup&gt;D</td>
<td>0 to 31</td>
<td>17.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Functional performance</td>
<td>LIFE-RIFT 1 (Work)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 to 5</td>
<td>4.12</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>LIFE-RIFT 2 (Interpersonal)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 to 5</td>
<td>3.96</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>LIFE-RIFT 3 (Satisfaction)</td>
<td>2 to 5</td>
<td>3.48</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>LIFE-RIFT 4 (Recreation)</td>
<td>1 to 5</td>
<td>3.14</td>
<td>1.22</td>
</tr>
</tbody>
</table>

<sup>a</sup>Represented as z-scores with respect to the normative group
<sup>b</sup>Represented as a total sum score
<sup>c</sup>Represented as the maximum value among multiple items within that domain
Correlations

Correlations among all neurocognitive variables, presented as z-scores, are reported in Table 3. Correlations among all measures used in this study are presented in Tables 4 -8. Two-tailed correlations were conducted among neurocognitive variables and symptoms since this was a novel analysis that was not informed by the literature. The remaining correlational analyses were one-tailed as they were informed by existing literature on other psychiatric disorders.

Table 3. One-tailed correlations among all neurocognitive variables

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCS</td>
<td>-</td>
<td>.83</td>
<td>.73</td>
<td>.39</td>
<td>.50</td>
<td>.67</td>
<td>.20</td>
</tr>
<tr>
<td>Sustained attention</td>
<td>(.001)</td>
<td>-</td>
<td>.60</td>
<td>.28</td>
<td>.29</td>
<td>.52</td>
<td>.04</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>(.001)</td>
<td>(.001)</td>
<td>-</td>
<td>.05</td>
<td>.11</td>
<td>.52</td>
<td>.27</td>
</tr>
<tr>
<td>Verbal working memory</td>
<td>(.018)</td>
<td>(.078)</td>
<td>(.394)</td>
<td>-</td>
<td>.25</td>
<td>.07</td>
<td>-.03</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>(.003)</td>
<td>(.068)</td>
<td>(.289)</td>
<td>(.097)</td>
<td>-</td>
<td>.33</td>
<td>-.23</td>
</tr>
<tr>
<td>Processing speed</td>
<td>(.001)</td>
<td>(.002)</td>
<td>(.002)</td>
<td>(.352)</td>
<td>(.437)</td>
<td>-</td>
<td>.14</td>
</tr>
<tr>
<td>Response inhibition</td>
<td>(.157)</td>
<td>(.428)</td>
<td>(.083)</td>
<td>(.123)</td>
<td>(.407)</td>
<td>(.328)</td>
<td>-</td>
</tr>
<tr>
<td>Set-shifting</td>
<td>(.001)</td>
<td>(.024)</td>
<td>(.005)</td>
<td>(.210)</td>
<td>(.389)</td>
<td>(.001)</td>
<td>(.216)</td>
</tr>
</tbody>
</table>

Table 4. Two-tailed correlations among neurocognitive and mood variables

<table>
<thead>
<tr>
<th></th>
<th>NCS</th>
<th>Sustained attention</th>
<th>Verbal learning</th>
<th>Verbal WM</th>
<th>Verbal fluency</th>
<th>Processing speed</th>
<th>Response inhibition</th>
<th>Set shifting</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAIa</td>
<td>-.12</td>
<td>-.16</td>
<td>-.26</td>
<td>.47</td>
<td>.08</td>
<td>-.33</td>
<td>-.40</td>
<td>-.26</td>
</tr>
<tr>
<td></td>
<td>(.524)</td>
<td>(.404)</td>
<td>(.173)</td>
<td>(.010)</td>
<td>(.665)</td>
<td>(.082)</td>
<td>(.037)</td>
<td>(.203)</td>
</tr>
<tr>
<td>MADRSa</td>
<td>.04</td>
<td>-.02</td>
<td>-.12</td>
<td>.27</td>
<td>.14</td>
<td>-.17</td>
<td>.07</td>
<td>-.03</td>
</tr>
<tr>
<td></td>
<td>(.856)</td>
<td>(.919)</td>
<td>(.549)</td>
<td>(.167)</td>
<td>(.471)</td>
<td>(.394)</td>
<td>(.713)</td>
<td>(.897)</td>
</tr>
<tr>
<td>HAMDa</td>
<td>-.02</td>
<td>-.15</td>
<td>-.20</td>
<td>.38</td>
<td>.34</td>
<td>-.35</td>
<td>-.01</td>
<td>-.17</td>
</tr>
<tr>
<td></td>
<td>(.912)</td>
<td>(.447)</td>
<td>(.300)</td>
<td>(.047)</td>
<td>(.075)</td>
<td>(.071)</td>
<td>(.952)</td>
<td>(.411)</td>
</tr>
</tbody>
</table>

a Higher score = more symptoms
Table 5. Two-tailed correlations among neurocognitive variables and symptom domains

<table>
<thead>
<tr>
<th>Table 5. Two-tailed correlations among neurocognitive variables and symptom domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-vegetative Symptoms&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Observed Mood&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.710)</td>
</tr>
<tr>
<td>Maladaptive Thought Patterns&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.651)</td>
</tr>
<tr>
<td>Neuro-vegetative Symptoms&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.231)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Higher score = more symptoms

Table 6. One-tailed correlations among neurocognitive and functioning measures

<table>
<thead>
<tr>
<th>Table 6. One-tailed correlations among neurocognitive and functioning measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSPA total&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Observed Mood&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.013)</td>
</tr>
<tr>
<td>Advanced Finances&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.018)</td>
</tr>
<tr>
<td>LIFE-RIFT 1 (Work)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.472)</td>
</tr>
<tr>
<td>LIFE-RIFT 2 (Interpersonal)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.298)</td>
</tr>
<tr>
<td>LIFE-RIFT 3 (Satisfaction)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.416)</td>
</tr>
<tr>
<td>LIFE-RIFT 4 (Recreation)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(p=.114)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Higher score = better competence

<sup>b</sup> Higher score = more functional impairment
Table 7. One-tailed correlations among mood variables and functioning

<table>
<thead>
<tr>
<th></th>
<th>HAMD c</th>
<th>MADRS c</th>
<th>BAI c</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSPA total a</td>
<td>.20</td>
<td>.43</td>
<td>-.13</td>
</tr>
<tr>
<td>(p=.159)</td>
<td>(p=.010)</td>
<td>(p=.250)</td>
<td></td>
</tr>
<tr>
<td>Advanced Finances a</td>
<td>-.03</td>
<td>.36</td>
<td>-.22</td>
</tr>
<tr>
<td>(p=.448)</td>
<td>(p=.035)</td>
<td>(p=.140)</td>
<td></td>
</tr>
<tr>
<td>LIFE-RIFT 1 (Work) b</td>
<td>.45</td>
<td>.55</td>
<td>.36</td>
</tr>
<tr>
<td>(p=.014)</td>
<td>(p=.003)</td>
<td>(p=.039)</td>
<td></td>
</tr>
<tr>
<td>LIFE-RIFT 2 (Interpersonal) b</td>
<td>.35</td>
<td>.51</td>
<td>.14</td>
</tr>
<tr>
<td>(p=.038)</td>
<td>(p=.003)</td>
<td>(p=.241)</td>
<td></td>
</tr>
<tr>
<td>LIFE-RIFT 3 (Satisfaction) b</td>
<td>.40</td>
<td>.57</td>
<td>.42</td>
</tr>
<tr>
<td>(p=.018)</td>
<td>(p=.001)</td>
<td>(p=.011)</td>
<td></td>
</tr>
<tr>
<td>LIFE-RIFT 4 (Recreation) b</td>
<td>.38</td>
<td>.58</td>
<td>.27</td>
</tr>
<tr>
<td>(p=.024)</td>
<td>(p=.001)</td>
<td>(p=.081)</td>
<td></td>
</tr>
</tbody>
</table>

a Higher score = better competence  
b Higher score = more functional impairment  
c Higher score = more symptoms

Table 8. One-tailed correlations among functional competence measures and real-world behaviour

<table>
<thead>
<tr>
<th></th>
<th>LIFE-RIFT 1 (Work) b</th>
<th>LIFE-RIFT 2 (Interpersonal) b</th>
<th>LIFE-RIFT 3 (Satisfaction) b</th>
<th>LIFE-RIFT 4 (Recreation) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSPA a</td>
<td>-.11</td>
<td>-.02</td>
<td>.22</td>
<td>.02</td>
</tr>
<tr>
<td>(p=.304)</td>
<td>(p=.458)</td>
<td>(p=.130)</td>
<td>(p=.459)</td>
<td></td>
</tr>
<tr>
<td>Advanced Finances a</td>
<td>.06</td>
<td>.05</td>
<td>.01</td>
<td>-.08</td>
</tr>
<tr>
<td>(p=.394)</td>
<td>(p=.411)</td>
<td>(p=.473)</td>
<td>(p=.341)</td>
<td></td>
</tr>
</tbody>
</table>

a Higher score = better competence  
b Higher score = more functional impairment
Neurocognitive Profile of TRD

A post-hoc repeated measures analysis of variance (ANOVA) was conducted to examine whether the neurocognitive domains differed significantly from one another. The repeated-measures ANOVA demonstrated that the neurocognitive domains were significantly different, Wilks’ lambda = .43, $F(6,18) = 3.96$, $p = .011$, partial $\eta^2 = .57$.

Follow-up pairwise comparisons between the neurocognitive domains were examined using paired-samples $t$-tests with a Dunn-Sidak correction of $1 - (0.95)^{1/21} = .002$. The follow-up pairwise comparisons were significant for verbal working memory and sustained attention ($p < .001$), verbal working memory and verbal learning ($p = .001$), verbal working memory and verbal fluency ($p = .001$), verbal working memory and information processing speed ($p = .001$), and verbal working memory and response inhibition ($p < .001$). All other neurocognitive domains were not statistically different from each other.

Neurocognition and Symptom Severity

The neurocognition composite score (NCS) was minimally and not significantly correlated with symptom severity on the MADRS, HAMD, or BAI. Differential patterns emerged when I examined the correlations among individual neurocognitive domains and symptom severity. Greater verbal working memory had a significant positive correlation with greater total HAMD score and total BAI score. Finally, better response inhibition significantly negatively correlated with the total BAI score. Moderate ($r_s > .30$) but not statistically significant correlations were observed between greater verbal fluency and greater total HAMD score, and faster information processing speed and total HAMD score and total BAI score. A family-wise Dunn-Sidak correction was applied, such that
anxiety and depressive symptoms were classified as separate families. The adjusted critical \( p \)-value for the correlations between the seven neurocognitive domains and anxiety (i.e., BAI) was \( 1 - (0.95)^{1/7} = 0.007 \) and the adjusted critical \( p \)-value between the seven neurocognitive domains and the two measures of depression (i.e., MARDS and HAMD) was \( 1 - (0.95)^{1/14} = 0.003 \). Therefore, none of the neurocognitive domains were significantly correlated with symptom severity measures after applying a Dunn-Sidak correction (see Table 4).

**Neurocognition and Depressive Symptom Domains**

Observed mood was significantly correlated with verbal working memory. However, this correlation no longer met significance after applying a Dunn Sidak correction \( (1 - (0.95)^{1/7} = 0.007) \). Correlations between neurovegetative symptoms and neurocognitive domains approached significance for sustained attention and information processing speed. Maladaptive thought patterns were not significantly correlated with any of the neurocognitive domains (see Table 5).

**Stepwise Regressions**

**Performance-based functional competence**

Stepwise regressions were conducted to determine the predictors of functional skill impairment (interpersonal and adaptive competence) and clinician rated real-world behaviour. Variables that were significantly correlated with the dependent variable were entered into one step and analyzed using a stepwise regression. The regression equation for interpersonal competence was significant with sustained attention entering first, \( F(1,25) = 6.49, p = .017, R^2_\Delta = .206, \) followed by MADRS total score \( F(2,24) = 7.15, p = .004, R^2_\Delta = .167 \). The regression equation for adaptive competence was significant with
age at baseline entering first, $F(1,23) = 6.48, p = .018, R^2\Delta = .220$, followed by set shifting, $F(2,22) = 7.26, p = .004, R^2\Delta = .178$. Refer to Table 9.

Table 9. Regression coefficients for interpersonal and adaptive competence

<table>
<thead>
<tr>
<th>Interpersonal competence</th>
<th>$B$</th>
<th>SE</th>
<th>Beta</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained attention</td>
<td>0.24</td>
<td>0.09</td>
<td>0.45</td>
<td>2.55</td>
<td>.017</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained attention</td>
<td>0.25</td>
<td>0.09</td>
<td>0.46</td>
<td>2.86</td>
<td>.009</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.03</td>
<td>0.01</td>
<td>0.41</td>
<td>2.53</td>
<td>.018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adaptive competence</th>
<th>$B$</th>
<th>SE</th>
<th>Beta</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline</td>
<td>0.22</td>
<td>0.09</td>
<td>0.47</td>
<td>2.55</td>
<td>.018</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline</td>
<td>0.21</td>
<td>0.08</td>
<td>0.44</td>
<td>2.62</td>
<td>.016</td>
</tr>
<tr>
<td>Set shifting</td>
<td>1.33</td>
<td>0.52</td>
<td>0.42</td>
<td>2.55</td>
<td>.018</td>
</tr>
</tbody>
</table>

Clinic rated real-world behaviour

Clinic rated real-world work behaviour, interpersonal relations, and general satisfaction were significantly predicted by the severity of depressive symptoms as measured on the MADRS, $[F(1,22) = 9.66, p = .005, R^2\Delta = .31], [F(1,25) = 9.04, p = .006, R^2\Delta = .27], [F(1,26) = 12.68, p = .001, R^2\Delta = .33]$, respectively. Recreation was significantly predicted by the symptom domain of observed mood and anxiety, $F(1,26) = 13.52, p = .001, R^2\Delta = .34$. Please refer to Table 10.

Table 10. Regression coefficients for real-world behaviour

<table>
<thead>
<tr>
<th>Work Behaviour</th>
<th>$B$</th>
<th>SE</th>
<th>Beta</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms</td>
<td>0.09</td>
<td>0.03</td>
<td>0.55</td>
<td>3.10</td>
<td>.005</td>
</tr>
<tr>
<td>Interpersonal Behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.07</td>
<td>0.02</td>
<td>0.52</td>
<td>3.01</td>
<td>.006</td>
</tr>
<tr>
<td>General satisfaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.05</td>
<td>0.01</td>
<td>0.57</td>
<td>3.56</td>
<td>.001</td>
</tr>
<tr>
<td>Recreation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed mood and anxiety</td>
<td>1.35</td>
<td>0.37</td>
<td>0.58</td>
<td>3.68</td>
<td>.001</td>
</tr>
</tbody>
</table>
Chapter 4

Discussion

The current study was the first of its kind to examine the relationships among neurocognition, symptoms, and functional outcomes in treatment-resistant depression (TRD). I sought to examine whether neurocognition was related to different symptom domains or to level of symptom severity, and to determine what neurocognitive, course of illness, and clinical variables predicted functioning in this unique population.

The neurocognitive profile of TRD

Examination of the neurocognitive profile of this sample suggested that individuals with TRD show mild to moderate impairments in global neurocognition and across all neurocognitive domains, with a superimposed severe impairment (mean $z$-score $= -1.67$) in verbal working memory. A repeated-measures analysis of the neurocognitive domains, suggested that individuals with TRD display a differential pattern of impairment in specific neurocognitive domains, rather than an over-arching global impairment. The emergence of impairments in specific neurocognitive domains is consistent with the literature on neurocognitive function in other severe chronic disorders, such as schizophrenia and bipolar disorder. For example, individuals with schizophrenia exhibit moderate to severe impairments (i.e., 1.5 to 3 standard deviations below the mean) in attention, working memory, verbal learning, language skills, executive functioning, and social cognition (Bowie & Harvey, 2005; Bowie et al., 2010). Similar to schizophrenia, individuals with TRD display deficits across multiple neurocognitive domains, however the magnitude of these deficits is smaller than those observed in schizophrenia.
The findings from the current study support a relationship between neurocognition and functioning that is similar in magnitude to other psychiatric illnesses. Compared to a sample of individuals with schizophrenia from Bowie et al., (2008), the magnitude of the correlation coefficients between neurocognition and interpersonal competence in TRD were similar to those observed in schizophrenia (range of correlation coefficients for schizophrenia = .34 -.47; Bowie et al., 2008). However, clinical symptoms were more related to real-world functioning in TRD than in schizophrenia. In schizophrenia, negative symptoms were strongly related to interpersonal behaviour (correlation coefficient = -.40), but positive symptoms and depression played very little role in predicting work and community behaviours (range of correlation coefficients = -.11 to -.25; Bowie et al., 2008). In contrast, depressive symptoms strongly predicted real-world functioning in the current TRD sample, across all domains including interpersonal, work, recreation, and general satisfaction.

The literature on neurocognitive deficits in MDD has proposed two hypotheses—the effort hypothesis and the cognitive speed hypothesis—as possible mechanisms for neurocognitive impairment. The effort hypothesis states that individuals with depression have difficulty on neurocognitive tasks that require effortful or elaborate processing, whereas the cognitive speed hypothesis states that slowed processing speed is the root cause of neurocognitive dysfunction. Research on this topic is mixed and there is evidence in support of both theories. As the current study employed neurocognitive measures that are both automatic and effortful, I visually examined whether the neurocognitive profile of the current TRD sample contributed to either hypothesis. The Trail Making Test Part A and Digit Symbol Substitution Task are both automatic speed
tasks, whereas the Trail Making Test Part B, Stroop Test, and Letter-Number Sequencing test are effortful tasks that engage working memory or executive functioning processes. As Letter-Number Sequencing (i.e., verbal working memory) was the most impaired neurocognitive domain in this sample, and was statistically significantly different from the other neurocognitive domains, the profile of neurocognitive impairment in the current study supports the effort hypothesis for treatment-resistant depression.

*The relationships between neurocognition and symptoms*

I hypothesized that greater neurocognitive impairment would be related to greater severity of clinical symptoms. The correlation between response inhibition and symptom severity was in the hypothesized direction, such that greater response inhibition was associated with less anxiety at the .05 level. However, an interesting, and seemingly paradoxical, finding emerged upon investigation of the verbal working memory domain. Better performance on a verbal working memory task was correlated with greater severity of depressive symptoms, greater anxiety, and greater observed mood and anxiety at the .05 level. This finding contributes to a growing body of literature linking working memory with some of the core features of depression, such as rumination. Rumination is a hallmark feature of depression that consists of reoccurring uncontrollable negative thoughts about oneself, the world, and the future. Unfortunately, I did not obtain a measure of rumination in the current study. However, rumination is a debilitating symptom of depression that is associated with vulnerability to the onset of depression, the recurrence of depressive episodes, and the maintenance of negative affect (Nolen-Hoeksema, 2000; Nolen-Hoeksema & Larson, 1999; Roberts, Gilboa, & Gotlib, 1998), and as such, is a likely feature of treatment-resistant depression. Interestingly, in the
current study, verbal working memory was (i) the most impaired neurocognitive domain; (ii) was significantly different from most other neurocognitive domains; and (iii) was correlated with more severe depression and anxiety. Researchers who study neurocognition and emotion have proposed that negative affect is related to more frequent negative thoughts, which in turn is related to the activation of mood-congruent representations in working memory (Isen, 1984; Siemer, 2005). Specifically, depression and rumination are associated with impairments in updating the contents of working memory, which can manifest as difficulty removing irrelevant negative material from working memory (Joormann & Gotlib, 2008). Switching attention away from, or exerting inhibitory control over, items currently held in working memory is difficult even for healthy individuals and increasingly large working memory loads decrease the speed at which participants can switch between tasks (Hester & Garavan, 2005). In fact, working memory tasks become more vulnerable to interruption and require greater concentration when working memory load is high (Gray et al., 2003; Kane & Engle, 2002) which can, in turn, interfere with effective problem solving. This phenomenon may provide insight into the perpetuation of the rumination cycle and may account for the surprising positive correlation between verbal working memory and severity of depressive symptoms.

The profile of functional impairment in TRD

Participants in the current study experienced moderate to severe impairments in work and interpersonal relations and mild to moderate impairments in recreational activities and general life satisfaction. This profile is comparable to another TRD sample reported by Petersen et al., (2004), which also employed a clinician-rated semi-structured
interview as a measure of functioning. In their study, clinicians rated a sample of patients with TRD as experiencing mild to moderate impairment in work-related activities, good to fair interpersonal relationships, poor level of involvement in recreational activities, and poor global social adjustment. Compared to the treatment-resistant sample from Petersen et al., (2004), the current sample experienced impairments in similar areas of psychosocial functioning, however, the magnitude of functional impairment may be slightly greater for the current sample.

**Predicting functional outcomes**

It is important to evaluate the role of neurocognition in predicting functional outcomes in TRD, as previous research in other psychiatric groups has shown that neurocognitive ability is critical to the acquisition of functional skills (Bowie et al., 2008; 2010). In the current study, better interpersonal competence was predicted by greater sustained attention and more severe symptoms of depression. The first part of this finding, concerning sustained attention, makes intuitive sense. Sustained attention is a neurocognitive skill that is necessary for following a conversation and is therefore likely to be an important asset in interacting successfully with others. The correlation between greater interpersonal skill and more severe depressive symptoms, on the other hand, is somewhat surprising. One would expect that more severe mood symptoms would be related to greater impairment in social competence (Kessler et al., 2003). A possible explanation, which requires further study, is that individuals with better social skills may have more insight into the discrepancy between their capabilities and their real-world performance. Their awareness of the discrepancy between their current interpersonal behaviour and that prior to their illness, or between their current interpersonal behaviour
and that of their peers, may be related to increased depressive symptoms. Replication of this finding in other TRD samples, and in MDD in general, is necessary and will be important in providing further insight into this unexpected effect. Future studies could examine possible mediators, such as motivation or dysfunctional attitudes, on the relationship between interpersonal competence and depressive symptoms. In the current study, none of the neurocognitive variables correlated with both interpersonal competence and depressive symptoms, so it is unlikely that neurocognition mediates this relationship.

Concerning adaptive competence, greater skill on the advanced finances task was predicted by older age at baseline and better set shifting. In a sample of individuals with treatment-resistant depression, it appears that the older someone is, the more likely they are to have had the opportunities and life experiences necessary for acquiring adaptive living skills, such as dealing with finances. Greater set shifting, or the ability to efficiently process information and switch between tasks, provides an advantage in the advanced finances task, and as such, may be an important treatment target for cognitive remediation programs aimed at improving functional competence in individuals with chronic depression.

All four of the real-world behaviour domains (work, interpersonal relations, satisfaction, and recreation) were predicted by depressive symptoms. Specifically, more impairment in work, interpersonal relations, and general satisfaction were associated with more severe symptoms of depression. More impairment in recreational activity was accounted for by greater observed depressive mood and anxiety. Interestingly, measures of one’s capability to complete tasks in a laboratory study are not significantly correlated
with real-world performance. Research in other chronic mental illnesses, such as schizophrenia, has shown that real-world behaviour does not have a one-to-one correspondence with competence. Often, factors other than competence can limit real-world performance. Common symptom-based rate limiters in the schizophrenia literature include positive and negative symptoms (Smith et al., 2002) and depressed mood (Bowie et al., 2006; 2010). Different intrinsic and extrinsic factors may predict a competence-performance discrepancy in TRD.

Limitations & Future Directions

The current study produced some interesting, albeit surprising, results. As this study has pioneered some of the first data regarding the relationships among neurocognition, symptoms, and functional outcomes in TRD, it has brought to light several important lessons and generated new ideas to take forth into future research. First and foremost, it is important to acknowledge that due to the sparse literature in this area, the theory that informed the hypotheses of this study stemmed from research on other psychiatric groups, such as schizophrenia. In addition to the fact that the schizophrenia literature abounds with research on neurocognition and functioning, the clinical and neurocognitive overlap between schizophrenia and TRD is striking, particularly when taking into account the relentless and chronic nature of both disorders. However, as this study has shown, the story is not the same in both populations. In schizophrenia, neurocognition plays a major role in both functional competence and real-world performance, however this relationship does not replicate in treatment-resistant depression. In TRD, neurocognition is an important predictor for interpersonal and adaptive competence, but is not significantly related to measures of real-world behaviour.
Interestingly, symptoms seem to be playing a much larger role in predicting real-world functioning in TRD compared to other disorders such as schizophrenia and bipolar disorder (Bowie et al., 2010). So the question that remains is, why are the results different for treatment-resistant depression? Despite the overlap in clinical and neurocognitive features across schizophrenia and mood disorders, what complex relationships are being overlooked in TRD by applying a schizophrenia framework?

Since there is hardly any literature on neurocognition and functioning in MDD, let alone TRD, this study, although limited, can provide some insight into future directions for research in this field.

There are several distinctions between schizophrenia and TRD, which could account for some of the unexpected findings in the current study. First, schizophrenia is a neurodevelopmental disorder with a deteriorating trajectory, whereas the symptoms of MDD are cyclical in nature even when severe and persistent. In general, individuals with MDD have better premorbid functioning, whereas individuals with schizophrenia tend to be low functioning prior to the onset of symptoms (APA, 2000). As such, individuals with MDD experience a more substantial drop in functioning at the onset of symptoms. Furthermore, individuals with MDD experience fewer disruptions in the absence of the negative symptoms, disorganized behaviour, and severe cognitive deficits that characterize schizophrenia. It is plausible that the neurocognitive deficits seen in MDD are trait rather than state-like. During the euthymic state, it is believed that the brain can repair itself and return neurocognitive functioning back normal (Hammar, Lund, & Hugdahl, 2003; Neu et al., 2005). It may be that different relationships would emerge between neurocognition and functioning in a euthymic sample. Finally, another potential
distinction between schizophrenia and depression that may mediate the relationship between neurocognition and functioning is stigma. Unfortunately, many individuals with psychological disorders experience some form of stigma during their lifetime (Stuart & Arboleda-Florez, 2001; Davis, 2006). An important question to address is how familial, spousal, and societal support differs between those with depression and those with schizophrenia, and what role that might play in determining functional outcomes and real-world behaviour. The aforementioned distinctions between the two disorders are important candidates for future research aiming to understand the complex relationships among neurocognition, symptoms, and functional outcomes in treatment-resistant depression.

An additional limitation to this study concerns the measure of real-world behaviour. Assessment of real-world behaviour is always difficult, and there is no gold standard measure. The instrument used in the current study was the LIFE-RIFT. Although the LIFE-RIFT is a clinician-rated tool, it is based on a semi-structured interview that elicits self-reports of functioning from the participant and is therefore, in essence, a self-report measure. As such, this measure is susceptible to biases in self-report, particularly since the negative attributional style of depressed thinking is known to affect recall of autobiographical memories (Kuyken & Dalgleish, 2011). The subjectivity of the LIFE-RIFT is a major limitation in the current study and may account for some of the unexpected relationships between real-world behaviour and other measures such as neurocognition or functional competence. Future work would strongly benefit from objective assessment of observed behaviour; for example, frequency counts of prosocial behaviours such as smiling, eye contact, body language, use of gestures, and
paralinguistic behaviour such as intonation of voice. In addition to the subjectivity inherent in this measure, the LIFE-RIFT reports only the highest score within each domain, and as such, may be missing some of the natural variance in functioning. For example, the interpersonal domain consists of ratings of the quality of relationship with spouse, children, extended family, and friends. In only taking the highest rating, the LIFE-RIFT may be ignoring important complexities in individuals’ everyday functioning.

It is important to note that in using z-scores to calculate the neurocognitive domains, it is possible that the statistical differences that emerged between these domains were due to differences among the various normative groups, as opposed to differences among the participants in the current study. Unfortunately, in clinical neuropsychology research, it is very difficult to obtain data on a single normative sample when empirically and theoretically selecting various neurocognitive domains from different neurocognitive batteries. As such, I was unable to test the veracity of this issue in the current study.

Finally, this study was limited by a very small sample size. Post-hoc power analyses were conducted using the program G*Power (Erdfelder, Faul, & Buchner, 1996). Power for all regressions was low (range .33 - .53). Replication of this research with larger sample sizes is necessary in order to confirm and expand upon the findings of this study.

Implications

The current study opened up new ground for research on the relationships among neurocognition, symptoms, and functioning in treatment-resistant depression. Individuals with TRD are a unique subset of those with MDD who suffer from chronic, persistent symptoms that are unresponsive to standard pharmacological and psychological
treatment. Better understanding of the predictors and factors associated with functional outcome in this group is of great importance in developing new approaches to treatment.

The current study revealed several exciting new findings. Verbal working memory plays a particularly important role in TRD. Verbal working memory appears to be the most impaired neurocognitive domain in this group, is significantly different from most other neurocognitive measures, and interestingly, greater verbal working memory capacity is related to more depressive symptoms and anxiety. Furthermore, neurocognition and depressive symptoms are both important in predicting functional competence (what one can do) but depressive symptoms are stronger predictors of functional performance (what one actually does in the real world). As such, there may be additional intrinsic or extrinsic factors, such as motivation, dysfunctional attitudes, or stigma, that are mediating the relationship between competence and performance and are worthy of investigation in future studies. Finally, neurocognition did emerge as a significant predictor of interpersonal and adaptive functioning. Research in other psychiatric groups has demonstrated that neurocognitive remediation therapy is effective at improving neurocognition and that these effects generalize to improved functioning in schizophrenia, bipolar disorder, and MDD (Wykes et al., 2009; Deckersbach et al., 2009; Naismith et al., 2011). Several studies have shown that cognitive remediation therapy can bolster the effects of other treatments, such as psychosocial intervention or occupational therapy (Bell et al., 2008; Hogarty et al., 2004; 2006). Results from the longitudinal aspect of this work will shed light on whether cognitive remediation is a unique treatment avenue that could provide some benefit to individuals with treatment-resistant depression. Treatment-resistant depression is a unique and debilitating
psychological disorder with a complex interplay among neurocognition, clinical symptoms, and functioning. Researchers and clinicians alike will need to take a unique approach to understanding functioning in order to develop novel and effective interventions and move forward in promoting both symptomatic and functional recovery in this group.
References


