COGNITION IN INDIVIDUALS AT FAMILIAL AND CLINICAL RISK FOR SEVERE MENTAL ILLNESS

by

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ABSTRACT

Severe mental illness (SMI) includes schizophrenia, bipolar disorder and severe and chronic major depressive disorder. SMI typically onsets early in the lifespan and causes significant impairments in functioning. Cognitive function has been proposed as a potential neurodevelopmental indicator of risk for development of SMI. However, the relationships between cognition and risk for onset of SMI in individuals at familial risk are not fully understood. This thesis aimed to investigate cognition in individuals at familial and clinical risk for SMI. In study 1, I examined cognition in 360 children and youth, and found that offspring of parents with psychotic SMI performed significantly worse on overall cognition, verbal intelligence, verbal working memory, processing speed, verbal learning and memory, verbal fluency and sustained attention. Sons and daughters of parents affected with non-psychotic SMI performed significantly worse than controls on verbal intelligence, visual memory and decision-making. The findings of study 1 indicate that mild cognitive impairment may be a marker of transdiagnostic familial risk for any form of SMI. Additional deficits in verbal cognition, verbal memory, verbal fluency, processing speed, and sustained attention may be markers of familial risk for psychotic SMI. In study 2, I investigated cognition as a potentially important indicator of neurodevelopmental disturbance and its association with propensity to experience psychotic symptoms in a cohort of 295 youth, 71 of whom reported definite psychotic symptoms. After accounting for age, sex and familial clustering, psychotic symptoms were associated with worse performance in overall cognition, verbal intelligence, visual memory, decision-making, spatial working memory, and set shifting. In study 3, I investigated cognitive performance as a potential etiological mechanism in the development of severe mental illness. In a 6-year longitudinal cohort of 309 youth, I found that onset of SMI was predicted by reduced overall cognitive performance, verbal intelligence, and sustained attention. These findings indicate that deficits in cognitive ability are associated with familial risk for psychotic SMI, propensity to experience psychotic symptoms, and new onsets of severe mental illness diagnoses in offspring. Impairments in overall cognition may be indicators of risk and targets for pre-emptive early interventions.

LIST OF ABBREVIATIONS USED

SMI	Severe Mental Illness
CHR	Clinical High Risk
FHR	Familial High Risk
MDD	Major Depressive Disorder
BD	Bipolar Disorder
SCH	Schizophrenia
SCH-A	Schizoaffective Disorder
WASI	Wechsler Abbreviated Scale of Intelligence
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children
DKEFS	Delis Kaplan Executive Function System
FSIQ	Full Scale Intelligence Quotient
EF	Executive Function
LNS	Letter Number Sequencing
CVLT	California Verbal Learning Test
VF	Verbal Fluency
BVRT	Benton Visual Retention Test
CMS	Children's Memory Scale
WMS	Wechsler Memory Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGT	Cambridge Gambling Task
SWM	Spatial working memory

IED	Intra/Extra Dimensional Set Shifting
SST	Signal Stop Task
RVP	Rapid Visual Processing
ToM	Theory of Mind
SPI-CY	Schizophrenia Proneness Instrument, Child and Youth Version
SIPS	Structured Interview for Prodromal Syndromes
FF	Funny Feelings Instrument
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
SADS-IV	Schedule for Affective Disorders and Schizophrenia
SCID-5	Structured Clinical Interview for DSM-5
DUSI	Drug Use Screening Inventory
ADHD	Attention Deficit Hyperactivity Disorder
SES	Socioeconomic status
SE	Standard error
95% CI	95% Confidence Interval
FORBOW	Families Overcoming Risks and Building Opportunities for Wellbeing

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CHAPTER 1

INTRODUCTION

1.1. Severe mental illness

Severe mental illness (SMI) includes schizophrenia and psychotic spectrum disorders, bipolar disorder, and major depressive disorder. SMI typically onsets in adolescence and early adulthood and causes serious disruption in educational and occupational achievement. Mental illness is a leading cause of global disability and is associated with shorter lifespan in affected individuals (De Hert et al., 2011; Vos et al., 2015). The strongest known risk factor for the development of SMI is a positive family history in a first-degree relative. Cognitive function has also been proposed as a potential neurodevelopmental risk factor in the development of SMI; however, this relationship is not yet well-understood. This thesis will examine cognition in individuals at familial and clinical risk for SMI.

1.2. Schizophrenia and psychotic spectrum disorders

Schizophrenia and psychotic disorders comprise a complex interaction of abnormal mental phenomena. Positive symptoms refer to the presence of abnormal mental process and include sensory hallucinations (tactile, auditory, visual, gustatory, olfactory experiences that are not present in reality) and delusions (strongly held false beliefs). Moreover, negative symptoms may also be present, and these refer to a reduction or absence of a normal mental function and include blunted affect or reduced emotional expression (e.g., facial expression, gestures), diminished flow or poverty of speech, and withdrawal from and/or lack of motivation or goal-directed behaviour. A third symptom domain typically affected is disorganization of speech (e.g., incoherent), thoughts (e.g., tangential and non-linear thought pattern), and behaviour (e.g., unusual actions and movement). In addition to these symptoms, psychotic disorders are associated with a

significant decline in premorbid functioning (e.g., self-care, social, occupational) (*Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*; Patel, Cherian, Gohil, & Atkinson, 2014). This thesis will investigate aims and hypotheses related to cognition in individuals with and without subclinical psychotic symptoms in a cohort enriched for familial risk for SMI.

1.3. Psychosis continuum

The psychosis continuum ranges from isolated subclinical psychotic symptoms with little to no impairment to individuals at ultra high risk with moderate impairment, to diagnosable psychotic disorders with severe functional impairment. However, the content of subclinical psychotic symptoms includes hallucinations and delusions which are indistinguishable from symptoms occurring in psychotic disorders (Kelleher et al., 2012a, 2012b). This conceptualization posits that subclinical psychotic symptoms occur along a continuum, which occur in 10-17% of children and 8% of adolescents in the general population, rather than a dichotomous disease model. Higher rates of subclinical psychotic symptoms have been reported in youth at familial risk for SMI (Fonville et al., 2015; Polanczyk et al., 2010; Zammit, Hamshere, et al., 2013; Zammit, Kounali, et al., 2013) For the purposes of this thesis, subclinical psychotic symptoms will be termed 'psychotic symptoms' throughout.

Psychotic symptoms in childhood and adolescence strongly predict the onset of severe psychiatric illness in adulthood, including schizophrenia, major mood disorders (Van Os, Jones, Lewis, Wadsworth, 1997; Sigurdsson, Fombonne, Sayal, Checkley, 1999), and suicide attempts (Poulton et al., 2000; Welham et al., 2009; Fisher et al.,

2013). In a large population-based birth cohort (n=761), Poulton et al. (2000) found that youth who reported psychotic symptoms at age 11 were more likely to develop schizophreniform disorder at age 26 than youth who reported no psychotic symptoms. Those with psychotic symptoms were then further subdivided into those with weak psychotic symptoms vs. those with strong psychotic symptoms. The weak psychotic symptom group was 5 times more likely to develop schizophreniform disorder at age 26 compared to individuals reporting no psychotic symptoms, and the strong psychotic symptom group was 16 times more likely to develop schizophreniform disorder by age 26, than youth who reported no psychotic symptoms, suggesting strong evidence for psychotic symptoms as a potential indicator of neurodevelopmental risk to later psychotic disorder. These findings remained after controlling for general childhood psychopathology, indicating specificity of risk. Therefore, psychotic symptoms represent early liability, and understanding their mechanisms of action in increasing risk for later psychotic disorder may provide targets for early intervention and prevention of SMI.

1.4. Psychotic symptoms as a transdiagnostic risk factor

There is growing evidence that psychotic symptoms are transdiagnostic, occurring commonly in mood and anxiety disorders (Wigman et al., 2012). Wigman et al. (2012) found that the prevalence of psychotic symptoms was doubled (27% versus 14%) in a large sample (n=3021) of young adults with major depressive disorder and any anxiety disorder compared to individuals without these disorders. In line with these findings, a network model analysis of transdiagnostic psychopathology indicated that psychotic symptoms strongly co-occur with anxiety symptoms (Wigman, de Vos, Wichers, van Os,

& Bartels-Velthuis, 2017). Bartels-Velthuis, van de Willige, Jenner, van Os, and Wiersma (2011) found that children who reported auditory vocal hallucinations at age 12 and 13 had 2 to 3 times increased odds of scoring within the clinical range on the Thought Problems scale (includes items such as "stares blankly", "can't get his/her mind off certain thoughts", and "repeats acts over and over") of the Child Behaviour Checklist at age 7-8. Increased psychopathology measured with the Child Behaviour Checklist Total Score at age 5 has also been shown to predict the development of psychotic symptoms at age 14 and 21 (Scott et al., 2009). The presence of psychotic symptoms in common mood and anxiety disorders is associated multiple co-morbidities (Kelleher et al., 2012), and poorer long-term prognosis (Wigman et al., 2012), highlighting that these are important transdiagnostic treatment targets.

1.5. Psychotic symptoms in individuals at high familial risk

The strongest known predictor of the development of severe mood and psychotic disorders is having an affected first-degree relative. Evidence of increased prevalence of psychotic symptoms in those at familial risk for SMI would help to further characterize potential combined risk factors and targets for early pre-emptive interventions. However, investigations of psychotic symptoms in individuals at familial risk for SMI have produced inconsistent results.

Several prospective studies have found higher prevalence of psychotic symptoms in children and adolescents at familial risk for SMI. In a large population-based longitudinal twin cohort, familial risk factors increased the likelihood of psychotic experiences. These family risk factors included maternal psychotic disorder, family

members admitted to psychiatric inpatient units, and family members with suicide attempts (Polanczyk et al., 2010). A higher correlation of psychotic symptoms was observed between monozygotic versus dizygotic twins, such that genetic effects accounted for 43% of the variance. Jeppesen et al. (2015) found increased risk of psychotic symptoms in sons and daughters of parents affected with psychotic disorders. The highest risk was found in offspring of parents affected with both hallucinations and delusions as part of their psychotic illness. However, the authors observed no association between offspring psychotic symptoms and parent history of nonpsychotic SMI.

Others have found no association between family history of psychotic disorder and psychotic symptoms, and only weak evidence of increased risk to experience psychotic symptoms in those with family history of major depressive disorder (Bevan Jones et al., 2016; Zammit et al., 2008). Mendez et al. (2019) found no increased risk of psychotic symptoms in children with parents affected with bipolar disorder. Bevan Jones et al. (2016) found no association between child psychotic symptoms and family history of psychotic disorder, parent psychotic symptoms, or family history of major depressive disorder severity. It is likely that lack of consensus regarding the assessment and definition of subclinical psychotic symptoms has contributed to inconsistent findings. The present thesis seeks to clarify the association between familial risk of psychotic and nonpsychotic SMI and increased propensity to experience psychotic symptoms.

1.6. Psychotic symptoms and cognition

It is well established that schizophrenia is a neurodevelopmental disorder (Murray & Lewis, 1987; Weinberger, 1987). The neurodevelopmental theory of

schizophrenia proposes that early subtle alterations in brain development occur in utero along with abnormalities in brain maturation, and potentially neurodegenerative processes throughout childhood and adolescence that together contribute to risk for psychotic disorders by early adulthood (McGrath, Féron, Burne, Mackay-Sim, & Eyles, 2009). Cognitive function may be an important indicator of neurodevelopment in individuals at risk for severe mental illness and psychotic disorder. Several studies suggest that deficits in cognition predate the onset of psychosis, while others propose that cognitive impairment may be associated with disease burden and medication. Impairment in cognitive function has been shown to progress throughout the clinical high risk prodrome in those who develop psychotic disorder (De Herdt et al., 2013; Meier et al., 2014).

Several reports indicate that psychotic symptoms are associated with mild impairment on cognitive tasks, in particular processing speed, attention, and executive functions including working memory (Fonville et al., 2015; Kelleher, Clarke, Rawdon, Murphy, & Cannon, 2013; Ziermans, 2013). Kelleher et al. (2013) reported mild processing speed and working memory deficits in a large population-based sample of adolescents reporting psychotic symptoms. Mollon et al. (2016) found that adults with psychotic symptoms exhibited mild-to-moderate cognitive deficits in verbal knowledge, working memory, and visual memory. Fonville et al. (2015) found that individuals with persistent, but not transient psychotic symptoms exhibited worse performance on a task of working memory compared with controls, highlighting the importance of longitudinal samples in this population. Blanchard et al. (2010) reported impairments in receptive

language, motor function, processing speed, and executive function in a small sample of adolescents who reported psychotic symptoms.

Mild cognitive impairment has also been associated with the development of psychotic symptoms. In the largest longitudinal sample to date (n=6784), Niarchou et al. (2013) found that processing speed ability at age 8 predicted subclinical psychotic symptoms at age 11. In the Environmental Risk Longitudinal Twin Study, a nationally representative birth cohort of over 2000 twins, full scale intelligence quotient (FSIQ) and the ability to interpret and understand the mental states of others, commonly referred to as Theory of Mind (ToM) (Frith, 2008) assessed at age 5 were associated with the development of psychotic symptoms at age 12 (Polanczyk et al., 2010). In the Dunedin birth cohort study, motor development, receptive language, and FSIQ assessed between age 3 and age 9 predicted the development of psychotic symptoms at age 11 (Cannon et al., 2002). There was no association between executive function scores and the development of psychotic symptoms. Previous investigations have not fully examined the potential associations between specific cognitive functions and psychotic symptoms utilizing a broad assessment of cognitive domains (i.e., executive function, verbal learning and memory, working memory, and attention).

Cognitive models of psychosis point to emotional salience as a key mechanism that can lead to the experience of psychotic symptoms (Underwood, Peters, & Kumari, 2015). Although current theories of psychosis indicate a substantial emotional component in the experience of subclinical psychotic symptoms, there has been little investigation of the relationship between emotional cognition (involving emotions, motivation, and rewards) or social cognition (including emotion recognition, processing, social

knowledge, and the ability to understand the mental states of others) and psychotic symptoms. Roddy et al. (2012) found that children who experienced psychotic symptoms performed worse on the Penn Emotion Recognition Test, which assesses facial emotion recognition. My colleagues and I found that mild impairment in hot executive function (or emotion-laden executive function) was associated with increased propensity to experience psychotic symptoms after controlling for age, sex, and cold executive function (or emotion-independent executive function) (MacKenzie et al., 2017).

Others have found no significant association between subclinical psychotic symptoms and cognitive performance. Mendez et al. (2019) found no association between worse performance on FSIQ and increased risk for psychotic symptoms in a large sample of offspring of parents affected with bipolar disorder. Similarly, Bevan Jones et al. (2016) found no association between FSIQ at 12 years of age and psychotic symptoms at longitudinal follow-up 13 and 29 months later. Inconsistent findings may be due to small sample sizes, lack of consistency in criteria for subclinical psychotic symptoms, and narrow range of cognitive tests administered.

There remains uncertainty in the literature as to whether cognitive impairment is associated with psychotic symptoms. One method for addressing this question is through the study of individuals with psychotic symptoms before the onset of SMI, serious functional impairment, and psychotropic medication. We address this gap in the literature by examining cognitive performance across a wide battery of domains in a cohort of individuals with and without psychotic symptoms. We hypothesized that overall impairment in cognitive function would be associated with psychotic symptoms in a longitudinal cohort enriched for familial SMI.

1.7. Cognition in individuals at high familial risk for SMI

Severe mental illness (SMI) includes schizophrenia, bipolar disorder, and severe major depressive disorder. SMI affects between 5-10% of the population (Kessler, Berglund, Bruce, 2001; *U.S. Census Bureau. 2010 Resident Population*, 2010) develops early in the lifespan, and causes serious impairments in lifelong functioning. Cognitive function is a core feature of SMI, and the strongest predictor of long-term functional outcome in patients with psychotic disorders (Green, 1996). Milder cognitive impairments have also been reported in first-degree relatives of individuals affected with SMI. Sons and daughters of parents affected with SMI may be exposed to genetic and environmental factors (e.g., trauma) that contribute to SMI, and are at a 1-in-3 risk of developing SMI by early adulthood (Rasic, Hajek, Alda, & Uher, 2014). Therefore, sons and daughters represent a unique population at high-risk for developing SMI in adulthood. Examining cognition as a neurodevelopmental risk factor for SMI may provide clues to the underlying etiology and assist with design of effective early interventions. Additional review of cognition in individuals at familial risk for SMI by diagnostic group and psychotic versus nonpsychotic phenotypes of SMI is further detailed below.

1.8. Cognition in individuals at familial high-risk for major depressive disorder

Major Depressive Disorder (MDD) is a common psychiatric disease with lifetime prevalence of 20% (Kessler et al., 2005). Cognitive impairments are common in individuals with MDD (McIntyre et al., 2013; Rock, Roiser, Riedel, & Blackwell, 2014) and persist after remission (Bora, Harrison, Yücel, & Pantelis, 2013; Shilyansky et al.,

2016). Some prospective studies suggest that impaired cognition predates the onset of MDD (Koenen, Moffitt, Roberts, & Martin, 2009; Scult et al., 2017) but others raise the possibility that cognitive impairment may be a consequence of depression, its comorbidity or its treatment (Moraros, Nwankwo, Patten, & Mousseau, 2017; Schaefer et al., 2017). One method of answering the question about the origin of cognitive impairments in depression is the study of unaffected relatives. First-degree relatives of people with MDD share half of the genetic variants with the affected individual that contribute to MDD risk and are at an increased risk of developing MDD themselves (Rasic et al., 2014; Sullivan, Neale, Ph, & Kendler, 2000). Presence or absence of cognitive impairment in unaffected relatives of individuals with MDD would be evidence that impaired cognition is a precursor or consequence of MDD respectively. However, investigations of cognition in first-degree relatives of individuals with MDD have been inconsistent, with some studies finding impaired cognitive performance relative to controls (Christensen, Kyvik, & Kessing, 2006; Hay et al., 2001; Whiffen & Gotlib, 1989; Winters, Stone, Weintraub, & Neale, 1981) and others finding no difference between groups (Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Santucci et al., 2014). It is likely that small sample sizes have limited the ability of previous investigations to detect small to moderate effects in this non-patient population due to lack of statistical power.

My colleagues and I completed a meta-analysis of 54 independent samples in more than 8000 individuals found that first-degree relatives of individuals with MDD performed worse than controls across all measures of cognition, and in 6 of 11 cognitive domains, including FSIQ, verbal intelligence, perceptual intelligence, memory, academic

performance and language (MacKenzie, Uher, & Pavlova, 2019). No differences were observed in the domains of attention, processing speed, executive function, emotion/social cognition, and psychomotor skills. Cognitive impairments were independent of relative type (offspring vs other first-degree relative), age, socioeconomic status, geographic region of sample, and publication year. The generalization of impairment across most cognitive domains suggests that familial liability to depression is associated with a broad impairment in cognition rather than a distinct cognitive profile.

1.9. Cognition in individuals at familial high-risk for bipolar disorder

Bipolar disorder is an SMI, characterized by episodes of mania (bipolar disorder I), hypomania (bipolar disorder II) and depression, affecting between 0.6 and 1.4% of the general population *(Diagnostic and Statistical Manual of Mental Disorders (DSM-5)).* Cognitive impairment is a common feature of individuals affected with bipolar disorder, and persists in euthymic mood states (Bora, Yucel, & Pantelis, 2009; Martinez-Aran et al., 2004). Moderate impairments have been consistently replicated in executive function, attention and memory (Bora et al., 2009).

Mild, intermediate impairments have also been shown in first-degree relatives at familial risk for bipolar disorder (Arts, 2007; Bora & Ozerdem, 2017; Bora & Ozerdem, 2017; Bora et al., 2009; Calafiore, Rossell, & Van Rheenen, 2018). Four meta-analyses of first-degree relatives of bipolar disorder have been completed within the last 12 years. In the first, Arts (2007) synthesized 14 studies. Findings indicated mild impairments within the domains of executive function and verbal learning and memory, which have been the most consistently replicated cognitive impairments in first-degree relatives of bipolar disorder. Verbal learning and memory was measured entirely with the California

Verbal Learning Test (Delis, 2000) and its analogues (Rey Auditory Verbal Learning Test (Bean, 2011)). It should be noted that story memory was not measured in this meta-analysis. Impairments in executive function were specific to executive control, measured with either Stroop (Delis, Kaplan, & Kramer, 2001a) or Trailmaking Test part B (Bucks, 2013).

The second meta-analysis compared cognitive performance in euthymic patients and their first-degree relatives (Bora et al., 2009). First-degree relatives and euthymic patients showed impairments within the domains of response inhibition, set shifting, executive function, verbal memory, and sustained attention. Euthymic patients with bipolar disorder in remission exhibited additional impairments in processing speed, visual memory and verbal fluency. Findings indicated that cognitive deficits appear to be trait and not state dependent, co-segregate in families, with intermediate, milder deficits observed between affected family members and healthy controls.

In a follow-up meta-analysis, Bora and Ozerdem (2017) meta-analyzed 18 studies of youth (mean age 10 to 25) at familial risk for bipolar disorder. First-degree relatives exhibited mild impairments in general intelligence, social cognition, visual memory, verbal memory, processing speed and sustained attention. No group differences were observed on executive function and working memory. The largest effect size was observed for social cognition, which was comprised of emotion recognition tasks and four separate Theory of Mind tasks. Although hot (or emotion-laden) executive function was measured in several studies (using the Cambridge Gambling task and Affective Go/No-Go task (Sahakian, 1992)), it appears that this data was not analyzed in the executive function analysis in the meta-analysis.

Bora and Ozerdem (2017) published a separate meta-analysis of social cognition in 15 separate samples of first-degree relatives of bipolar disorder compared with healthy controls. Social cognition was assessed with either emotion recognition accuracy or Theory of Mind (ToM) performance. First-degree relatives exhibited moderate impairment in ToM. However, group differences in emotion recognition were small and nonsignificant after accounting for a test of publication bias. This indicates that ToM may be a marker of liability to bipolar disorder in individuals at familial risk.

The largest existing sample of offspring of parents with bipolar disorder was published since the last meta-analysis (Hemager et al., 2018). Hemager et al. (2018) found that 7-year old children of parents affected with bipolar disorder do not exhibit cognitive impairments relative to offspring of control parents. These findings suggest that cognition may not be impaired in early childhood. Alternatively, differences in cognitive abilities in earlier development may be too subtle to reliably detect. Considering the aforementioned meta-analyses primarily analyzed individuals aged 10 and above, these findings may indicate that mild cognitive dysfunction may have a later developmental onset in those at familial risk for bipolar disorder compared with children at familial risk for schizophrenia.

A previous systematic review of cognition literature in first-degree relatives of bipolar disorder highlights the lack of language research in this population (Balanza-Martinez et al., 2008). The investigation of language could be particularly useful, as the consistent finding of verbal learning and memory impairment suggests a potential role for receptive and expressive communication skills, which may be particularly impaired in those at familial risk for bipolar disorder. Previous studies in this field have been

characterized by very small sample sizes which can be especially problematic when exploring the potential for small to medium effect sizes in this unique nonpatient population. Large, well-characterized longitudinal cohorts are needed to help direct the investigation of specific cognitive domains and the potential role for language impairments in individuals at familial risk for bipolar disorder.

1.10. Cognition in individuals at familial high-risk for schizophrenia

Schizophrenia and psychotic spectrum disorders affect approximately 0.3 to 1% of the general population (*Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*). Schizophrenia and psychotic disorders include positive symptoms (i.e., hallucinations and delusions), negative symptoms (i.e., avolition, reduced emotional expression), disorganization (i.e., incoherent speech, tangential thought process, atypical behaviours), and markedly reduced social and role functioning. Marked cognitive impairment has been well documented in individuals affected with schizophrenia, which persists after remission of positive symptoms (Caldiroli, Buoli, Serati, Cahn, & Altamura, 2016; Wang et al., 2015). In an effort to clarify the large body of literature completed in the field of cognition in schizophrenia, and to generate a consensus battery that could be utilized in clinical trials targeting treatment, the National Institue of Mental Health created a Neurocognition Committee, entitled the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) committee. In 2006, the initial consensus battery of 7 core cognitive domains was published, including (1) processing speed, (2) attention/vigilance, (3) working memory, (4) verbal learning and memory, (5) visual learning and memory, (6) reasoning and problem solving, and (7) social cognition

(Nuechterlein & Green, 2006; Nuechterlein et al., 2008). The MATRICS consensus battery has also been employed by researchers to guide investigations of cognitive impairment in first-degree relatives at familial risk for schizophrenia.

Several meta-analyses investigating cognitive performance in first-degree relatives of people affected with schizophrenia have been published in the last 15 years. The initial, by Sitskoorn, Aleman, Ebisch, Appels, and Kahn (2004) synthesized 37 studies and found small-to-medium effect size differences between relatives and controls in the domains of verbal memory, executive function, processing speed, working memory, verbal fluency, sustained attention, and visual memory. A follow-up meta-analysis was completed the following year, focused entirely on tests of executive functions in people with schizophrenia and their first-degree relatives (Szoke et al., 2005). First-degree relatives performed worse than controls on all tests of executive functions (small to medium range). However, the largest effect sizes were observed in tests of verbal executive function. Snitz, MacDonald, and Carter (2006) replicated earlier findings with a follow-up meta-analysis of 58 studies and found that first-degree relatives performed worse than controls in the domains of sustained attention, working memory, verbal fluency, and verbal memory. Jameson, Nasrallah, Northern, and Welge (2011) completed a narrowly focused synthesis of performance on the Wisconsin Card Sort Task (M. McGrath, 2011) as a measure of executive function in 23 studies comparing first-degree relatives with controls. Relatives performed worse on two dimensions, completing less categories overall and making greater perseverative errors. A separate meta-analysis of social cognition was completed by Lavoie et al. (2013) including 29 studies in adult first-degree relatives. Medium effect sizes differences indicating worse performance in

individuals at familial risk compared with controls were reported within the domains of mentalizing (i.e., attribution of mental states to specific characters via the expression of facial, bodily or verbal communication), emotional processing (i.e., emotion recognition via facial expression or prosody of speech), and social perception (i.e., ability to make social judgements). Finally, Bora (2017) meta-analyzed 19 studies of cognition in first-degree relatives of schizophrenia and found that relatives performed worse than controls (moderate effect sizes) in all cognitive domains, including FSIQ, verbal memory, visual memory, working memory, processing speed, sustained attention, executive function, and verbal fluency.

We completed systematic review of the literature published since the most recent meta-analysis (articles published between December 2016 and May 2019). Our systematic search yielded 9 studies, 5 of which were focused on emotion or social cognition, 6 reported cognitive battery results, and 5 reported FSIQ. With regard to emotion cognition, 2 of 5 studies reported worse performance on emotion perception and emotion recognition tasks (Horton, Bridgwater, & Haas, 2017; Kother, Lincoln, & Moritz, 2018), while the remaining 3 studies found no difference in emotion cognition performance of first-degree relatives compared with controls.

Cognitive battery findings were also mixed. Fernandez et al. (2018) found no difference in FSIQ or verbal memory performance of first-degree relatives compared with controls. Similarly, Kother et al. (2018) found no difference in verbal cognition, working memory, processing speed and executive function in first-degree relatives compared with controls. de la Serna et al. (2017) and colleagues reported no difference in verbal IQ, perceptual IQ, and processing speed index; however, first-degree relatives

performed worse than controls on tests of working memory, verbal learning delay recall, and visual memory. Frajo-Apor et al. (2017) reported no differences within the Brief Assessment of Cognition in Schizophrenia (BACS; verbal fluency, motor skills, processing speed, reasoning and problem solving, verbal memory and working memory; based on four of the seven cognitive domains in the MATRICS) battery, with the exception of worse performance on the executive function task, Tower of London, in first-degree relatives compared with controls. Aydin et al. (2017) reported that first-degree relatives performed worse than controls on tests of verbal fluency, processing speed, and executive function. Finally, in the largest dataset to date within this field of literature, Hemager et al. (2018) found that children of parents affected with schizophrenia performed significantly worse than controls on processing speed, working memory, executive function, and visual memory.

It is likely that small sample sizes have limited the ability of previous investigations to detect small-to-medium effect sizes in this nonpatient population. Three of the nine reviewed studies in a systematic search of the literature published since December 2016 included samples with less than 30 first-degree relatives, and 8 of 9 included less than 60 first-degree relatives. An updated meta-analysis with a composite sample that provides adequate statistical power to investigate cognition in first-degree relatives of individuals with schizophrenia is needed to further clarify this field of literature.

1.11. Cognition in individuals at familial high-risk for transdiagnostic psychotic SMI

Psychotic forms of SMI are associated with greater cognitive impairment than non-psychotic SMI (Brasso & Bornstein, 1999; Jimenez-Lopez et al., 2017; Lee et al., 2013; McCarthy, Weiss, Segovich, & Barbot, 2016; Trisha, Golnoush, Jan-Marie, Torres, & Yatham, 2018; Zaninotto et al., 2015). Brasso and Bornstein (1999) found that individuals with psychotic major depressive disorder showed significantly greater deficits relative to individuals with non-psychotic major depressive disorder on verbal and nonverbal cognition, as well as working memory, verbal memory, executive function, and attention tasks. Jimenez-Lopez and colleagues found that individuals with bipolar disorder with psychotic features performed significantly worse than those with non-psychotic bipolar disorder in the domain of working memory (Jimenez-Lopez et al., 2017). Trisha et al. (2018) found that individuals with bipolar disorder with a history of psychosis performed significantly worse than individuals with bipolar disorder with no history of psychosis in the domains of verbal memory, executive function, and cognitive flexibility. Individuals with mood-incongruent psychotic features (i.e., psychotic illness outside the context of episodes of mania and depression) performed significantly more poorly on tasks of attention, processing speed, and executive function tasks, compared with individuals with psychotic features in the context of their mood episodes (i.e., mania and/or depression).

Thus far, investigation of cognition in individuals at familial risk for SMI has been largely disorder-specific (i.e., major depressive disorder, bipolar disorder, schizophrenia) (Bora, 2017; Bora et al., 2009; Gur, 2007; Snitz et al., 2006). However, current models support a significant degree of overlap between genetic, clinical and cognitive characteristics for the spectrum of SMI and psychotic illness (Cuthbert & Insel,

2010). To our knowledge, this dissertation is the first study to investigate cognitive functioning in offspring of parents with psychotic and nonpsychotic transdiagnostic SMI. This thesis aims to investigate the relationship between transdiagnostic psychotic and nonpsychotic SMI and offspring cognitive function. We assessed cognition with standardized paper-and-pencil tests, and computerized tests from the Cambridge Automated Neuropsychological Test Battery (CANTAB). We hypothesized that offspring of parents with SMI would show mild cognitive impairment compared to controls with no family history of SMI. Based on previous literature, we additionally hypothesized that offspring of parents with transdiagnostic psychotic SMI would show more widespread cognitive impairments than offspring of parents with non-psychotic SMI.

1.12. Cognitive performance as a predictor of SMI in high familial risk

Evidence from large, prospective birth cohort studies indicates that lower IQ in childhood and adolescence predicts psychotic SMI in adulthood. In the aforementioned Dunedin longitudinal birth cohort, 11-year old children who went on to develop schizophreniform disorder exhibited significantly poorer receptive language ability and general intelligence scores over repeated assessments (5 assessments between age 3 and 11 years) (Cannon et al., 2002). In the National Survey of Health and Development (England, Scotland, and Wales), worse performance on IQ tests assessed at aged 11 and 15 was associated with development of schizophrenia in adulthood; no association was observed with IQ performance at age 8, however (Jones, Rodgers, Murray, & Marmot, 1994). Lower performance on tests of educational achievement at all ages (8, 11, and 15)

was also associated with the development of schizophrenia in adulthood. Similarly, within the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, individuals who went on to develop psychotic disorder showed gradually increasing cognitive impairments at 18 months, 4 years, 8 years, 15 years and 20 years of age (Mollon, David, Zammit, Lewis, & Reichenberg, 2018). In the Copenhagen Perinatal Cohort, cognitive function at age 12 and age 18, and decline in performance between these ages was associated with development of schizophrenia in adulthood (Osler, Lawlor, & Nordentoft, 2007). This pattern of results indicates that cognitive impairment may represent early risk for SMI in adulthood. Previous investigation has focused on the development of psychotic disorder and there has been little investigation of risk for the development of non-psychotic SMI. Although characterizing specific cognitive domains may provide helpful clues to the etiology and prevention of SMI, existing research has primarly focused on FSIQ.

Other prospective studies have found no association between cognitive performance and onset of non-psychotic SMI. Schaefer et al. (2017) found that IQ assessed at age 12 with two subtests of the Wechsler Intelligence Scale for Children (Matrix Reasoning and Information) did not predict onset of major depressive disorder in adulthood. In the National Child Development population-based birth cohort, lower IQ assessed at age 7 and 11 was associated with the development of schizophrenia, but not affective disorders in adulthood (Schulz, Sundin, Leask, & Done, 2014). Zammit et al. (2004) found that lower premorbid IQ in a large sample of male Swedish conscripts (1969-1970) was associated with increased risk for severe depression. However, both low IQ scores and average IQ scores were predictive of the development of schizophrenia,

indicating a protective factor for individuals in the high IQ score group. The authors also observed no association between IQ scores and the development of bipolar disorder (Zammit et al., 2004). Reichenberg et al. (2002) found an association between worse performance on IQ scores and later development of schizophrenia in the Israeli Draft Board Registry. In line with the findings of Zammit and colleagues (2004), Reichenberg et al. (2002) also reported no association between IQ scores and the development of nonpsychotic bipolar disorder.

These inconsistent findings may be due to differences in research design and narrow range of cognitive tests administered. Sample sizes were large, therefore differences in findings are unlikely attributable to lack of statistical power. In addition, familial risk was not reported within these studies, therefore it is unknown whether individuals also had familial risk factors. There is currently no data on cognitive performance as a predictor of SMI onset in individuals at familial risk. We hypothesized that overall cognitive performance would predict new onset of an SMI diagnosis in a longitudinal sample of individuals at familial risk.

1.13. Overview

It is not yet clear whether cognitive impairment precedes SMI in those at risk. This dissertation will address these gaps in the literature by investigating cognitive performance across a wide battery of domains in a cohort of individuals at clinical and familial risk for SMI. In Study 1, we hypothesized that offspring of parents with SMI would show mild cognitive impairment compared to control offspring with no family history of SMI. Based on previous literature, we additionally hypothesized that offspring

of parents with transdiagnostic psychotic SMI would show greater and more widespread cognitive impairments than offspring of parents with non-psychotic SMI. In Study 2, we predicted that mild impairment in overall cognitive function would be associated with propensity to experience psychotic symptoms. As a secondary hypothesis for Study 2, we hypothesized that the prevalence of psychotic symptoms would be greatest in those at familial risk for psychotic SMI and intermediate in those at familial risk for nonpsychotic SMI compared with sons and daughters of control parents. This sample is enriched for familial risk for psychotic and nonpsychotic severe mental illness, therefore it is the ideal sample to test these associations. In Study 3, we hypothesized that overall cognitive performance would predict new onset of an SMI diagnosis in a longitudinal study of sons and daughters of parents affected with SMI.

CHAPTER 2
METHODS

2.1. Sample

All participants within this thesis were drawn from the larger *Families Overcoming Risks Building Opportunities for Wellbeing* (FORBOW) study, a longitudinal cohort enriched for SMI (Uher et al., 2014). Sons and daughters of parents with SMI were recruited through mental health clinicians in Nova Scotia, Canada, who systematically inquired whether patients with psychotic and major mood disorders had children in the eligible age range (for FORBOW study 1-24 at baseline; for this thesis 6-24). Offspring participants were included regardless of whether or not they demonstrated current psychopathology. Partnership with the Nova Scotia Department of Community Services enabled enrollment of all biological parent and offspring, including sons and daughters not in the care of their biological parents. Control parents were recruited through local school boards and other community organizations (e.g., daycares).

2.2. Procedure

Participants completed cognitive tasks and clinical interviews at 12-month intervals, with a mean of 2.73 (S.D. = 1.51) assessments completed per participant (annual follow-up range 1-6). Participants and their parents attended research asesssments every 12-months (or within 1 month earlier or later). Trained research staff blinded to parent psychopathology assessed offspring. Assessors of parents were also blinded to offspring psychopathology. The cognitive protocols were designed in consultation with psychologists in the field (Dr. Larry Seidman, Dr. Elsa Gilbert, Dr. Jens Richardt Mollegaard Jepsen, Dr. Aja Neergaard Greve, Dr. Barbara Pavlova). Particular attention was paid to designing protocols that minimized practice effects (e.g., no repetition of executive function tests, WASI completed every 2 years rather than every

year) and were not overly burdensome with respect to assessment length (i.e., maximum length between 2-2.5 hours including breaks). Cognitive assessments were always completed prior to clinical interviews to avoid fatigue effects. All cognitive tests were administered in the same order based on cognitive protocols I developed in consultation with several psychologists and the research group principal investigator, Dr. Rudolf Uher. There were no verbal tasks administered during the story delay (Cohen, 1997; Wechsler, 1997). All participants were offered at least two, ten-minute breaks. However younger participants may have requested and received additional brief movement breaks during cognitive assessments. Additional detail regarding the annual research assessments are included in **Table 2.1.** For a complete list of cognitive protocols by assessment visit, see section Appendix A.

Table 2.1. Overview of annual assessment protocol measures included in this thesis

Assessment		**1**	**2**	**3**	**4**	**5**	**6**	**Age Range**
Cognitive Measure	**Cognitive Test**							
WASI-II		X		X		X		6+
WISC/WAIS	LNS	X		X				6+
WISC/WAIS	Coding	X	X	X				6+
CVLT	Trials 1-5	X						6+
D-KEFS	Verbal Fluency (Standard Form)	X			X			8+
D-KEFS	Verbal Fluency (Alternate Form)		X					8+
CMS/WMS	Stories Immediate	X		X				6+
CMS/WMS	Stories Delay Recall	X		X				6+
BVRT	FORM C			X				8+
CANTAB	CGT	X						8+
CANTAB	SWM	X						7+
CANTAB	RVP		X			X		6+
CANTAB	SST			X				8+
CANTAB	IED				X			7+
Clinical Interview								
K-SADS		X	X	X	X	X	X	6+

SCID-5	X	X	X	X	X	X	18+
SPI-CY	X	X	X	X	X	X	8+
FF	X	X	X	X	X	X	7+
SIPS	X	X	X	X	X	X	12+
Self-Report							
DUSI	X	X	X	X	X	X	11+

Note. WASI-II = Wechsler Abbreviated Scale of Intelligence, Second Edition, WISC = Wechsler Intelligence Scale for Children, WAIS = Wechsler Adult Intelligence Scale, CVLT = California Verbal Learning Test, CMS = Children's Memory Scale, BVRT = Benton Visual Retention Test, CANTAB = Cambridge Neuropsychological Test Automated Battery, K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia, SCID-5 = Structured Clinical Interview for DSM-5, SPI-CY = Schizophrenia Proneness Instrument Child and Youth Version, FF = Funny Feelings Instrument, SIPS = Structured Interview for Prodromal Syndromes, DUSI = Drug Use Screening Inventory, LNS = Letter Number Sequencing, Coding = Digit Symbol Coding, CGT = Cambridge Gambling Task, SWM = Spatial Working Memory, RVP = Rapid Visual Processing, SST = Signal Stop Task, IED = Intra/Extra Dimensional Set Shifting.

2.3. Cognitive Battery

2.3.1. General Intelligence

Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

General cognitive ability was assessed using the four subtest version of the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II(Wechsler, 1999)). The WASI-II is an individually administered assessment of intelligence of participants aged 6 through 90 years. The WASI-II was administered by trained research staff and graduate students with neuropsychological coursework or research-related training. The WASI-II provides a valid and reliable assessment of full-scale intelligence quotient (FSIQ). There are four subtests on the WASI-II that are combined to measure FSIQ: Block Design, Vocabulary, Matrix Reasoning, and Similarities.

2.3.2. Verbal Learning

California Verbal Learning Test (Delis, 2000)

Verbal declarative memory was assessed using the California Verbal Learning Test, Children's Version (CVLT-C(Delis, Kramer, Kaplan, & Ober, 1994)) in ages 6-15, and with the California Verbal Learning Test Second Edition (CVLT-II (Delis, 2000)) in ages 16-24. Participants were presented with a 16-word list over 5 consecutive trials. After administering each word list, the assessor recorded the participant's verbal responses verbatim. Research staff audio-recorded participant responses to ensure accurate scoring. Audio recordings of CVLT responses were immediately deleted following the scoring of this test. Although the CVLT has additional subtests, only Trials 1-5 (List A) were administered to participants. This choice was made a priori after consultation with leading psychologists in the field of familial and clinical risk for

psychosis. The standardized score for performance across Trials 1-5 was included in analyses.

2.3.3. Verbal story memory

Children's Memory Scale – Story Memory (Cohen, 1997)

Verbal narrative memory was assessed with the Children's Memory Scale Story Memory subtest. The Children's Memory Scale is a reliable and valid comprehensive test of children's memory normed for use with children aged 5 to 16. Only the Story Memory subtests were administered (immediate and delay recall). The Story Memory subtest measures children's capacity to recall meaningful information that is presented in a sequential story format. In this subtest the assessor reads the child two stories, then after each story the child is asked to retell the story to the examiner. The delayed recall component of Story Memory was administered 25 minutes following the initial story administration. The retelling of the story was audio recorded, later transcribed and then double scored by trained research staff and graduate students blind to parent diagnoses and symptomatology. The audio recording of the participant responses were immediately deleted following the transcription. Based on an *a priori* analysis plan, the primary outcome variable for Story Memory was the mean of the immediate and delay recall performance variables.

Wechsler Memory Scale (WMS; (Wechsler, 1997)

We measured verbal narrative memory in participants aged 16-24 with the Logical Memory I and II subtests of the Wechsler Memory Scale. Participants were read a short story and asked to verbally retell as many details as possible both immediately following the story (Logical Memory I), and after a 25-minute delayed recall (Logical

Memory II). The retelling of the story was audio recorded and later transcribed and scored by trained research staff and graduate students blind to parent diagnoses and symptomatology. Based on an *a priori* analysis plan, the primary outcome variable for the Logical Memory Test was the mean of the immediate and delay recall performance variables.

2.3.4. Visual Memory

Benton Visual Retention Test (BVRT (Benton, 1974)

Visual memory was assessed with the Benton Visual Retention Test, Administration A. Participants were shown an abstract design for 10 seconds, then the design was covered and participants immediately reproduced the design from memory in standardized test response booklets. The test includes 10 cards administered in sequence with increasing difficulty. There are two primary outcome variables of this test: 1) Total correct: participants receive a 0 or 1 with 0 indicating at least one error made and 1 indicating no error present, 2) Total errors: errors were recorded into 6 categories (omissions, distortions, perseverations, rotations, misplacements, and size errors). Based on an *a priori* analysis plan, we measured BVRT performance using the total correct variable.

2.3.5. Processing Speed

Digit Symbol Coding

Processing speed was measured using the Digit Symbol Coding subtest of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV (Wechsler, 2003)) for child participants aged 6-15, and the Wechsler Adult Scale of Intelligence – Fourth Edition (WAIS-IV (Wechsler, 2008)) for participants aged 16-24. This 2-minute task

requires the individual to copy abstract geometric shapes according to their corresponding number as quickly as possible. The participant is required to complete the task sequentially, line by line from left to right top to bottom. There are two outcomes of this task: 1) the number of correct responses and 2) the number of errors. The *a priori* primary outcome variable was the number of correct responses.

2.3.6. Cold Executive Function

Letter Number Sequencing

Auditory working memory was assessed with the Letter Number Sequencing subtest of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV(Wechsler, 2003)) and the Wechsler Adult Scale of Intelligence (WAIS (Wechsler, 2008)). In this task, the participant is read an increasingly complex series of numbers and letters. The examiner instructed the participant to repeat the numbers first, from smallest to largest, then the letters, in alphabetical order (e.g., sequence P-9-A-7 is reordered to correct response 7-9-A-P). The primary outcome variable was the age standardized number correct responses.

Verbal Fluency

We measured verbal fluency with the Letter Fluency subtest of the Delis Kaplan Executive Functioning System (Delis, Kaplan, & Kramer, 2001b). In the Letter Fluency tasks, participants are required to say as many words as they can in 1 minute for each of three letters (e.g., T-E-W). Participants are instructed not to use names, numbers, or the same root word with different tenses after the original root word has been stated (e.g., sing, sings, singing). The primary outcome variable was the number of correct responses.

Spatial Working Memory (SWM (Sahakian, 1992))

We measured spatial working memory with the SWM subtest of the Cambridge Neuropsychological Test Battery (CANTAB; (Sahakian, 1992). Participants were required to search for a blue token 'hidden' under a varied number of boxes (between 3 and 10 boxes on increasingly difficult trials). Participants are explicitly told that "once a blue token has been found under a box, there will never be one in there again, so you must not go back to it". It is therefore necessary for the participant to remember which box they have found a token in while searching.

SWM includes 5 primary variables: between search errors, within search errors, double errors, total errors, strategy. Total errors are calculated as the number of times a box is selected that is certain not to contain a blue token and therefore should not have been selected by the participant, i.e., between errors + within errors – double errors. Between errors are defined as times the participant revisits a box in which a token has been previously found. Within errors are defined as the number of times a participant revisits a box already found to be empty during the same search. Double errors are recorded in instances when a participant commits an error that can be categorized as both a within and a between error. Strategy is defined as following a predetermined sequence by beginning with a specific box, and then, once a blue token has been found, to return to that box to start the new search sequence. It is calculated by counting the number of times the participant begins a new search with a different box (6 and 8 box trials only). Based on an *a priori* analysis plan, the primary outcome variable was SWM Total Errors.

Intra-Dimensional/Extra-Dimensional Set-Shifting (IED; *(Sahakian, 1992))*

We assessed set shifting with the Intra-dimensional/extra-dimensional set-shifting task subtest of the CANTAB. Participants are required to learn the correct rule between

two sets of abstract stimuli (purple shapes and white lines) using feedback provided during the computerized task. The rule was changed after the participant selected the correct choice on 6 consecutive trials. The program ended after 50 incorrect choices. The test consists of 9 stages with increasing difficulty. In stages 1-5 participants had to correctly choose between two shapes and ignore overlapping lines. Stage 6 and 7 involved intra-dimensional set shifting (i.e., shifting between shape patterns) and required participants to correctly identify the rule with the introduction of new set of shapes. Stage 8 involved extra-dimensional set shifting and required participants to shift their attention away from the previously relevant stimuli (i.e., shapes) and correctly select the other stimuli (i.e., lines). Stage 9 also involved extra-dimensional set shifting with a focus on reversal learning. Participants were required to correctly identify the previously incorrect line pattern in stage 8. Outcome variables for the Intra-Dimensional/Extra-Dimensional Set-Shifting task involve total errors, number of trials completed, number of stages completed, and latency to response. Based on an *a priori* analysis plan, the primary outcome variable was IED Total Errors.

Stop Signal Task (SST (Sahakian, 1992))

We measured participant ability to inhibit a response using the Stop Signal Task of the CANTAB. There are two phases of this task. In phase 1, the participant is shown arrows on a computer screen pointing in either the left or right direction and the participant must press the corresponding left or right button on the press pad "as quickly as they can". In phase 2, the participant is instructed to continue pressing the corresponding buttons as quickly as they can; however, the participant is instructed to not press either button whenever an audible beep is present. Seventy-five percent of the trials

are ‘go’ trials (no audible beep), and 25% require the participant to inhibit a response when they hear the beep. Participants complete 5 blocks with 64 trials each in phase 2. Following each block, the computer provided a graph indicating overall performance (combination of ‘go’ reaction time and inhibition trial errors). Participants were verbally instructed to “continue responding as fast as you can and stop whenever you hear the beep” following each block. Based on an *a priori* analysis plan, the primary outcome variable was total correct on stop and go trials.

2.3.7. Hot Executive Function

Cambridge Gambling Task (CGT (Sahakian, 1992))

We measured decision-making in the context of uncertain rewards and losses with the CGT subtest on the CANTAB. The CGT involves the participant using a touch screen tablet. At each trial, the participant is presented with a row of 10 red and blue boxes at the top of the screen. The number of boxes of each colour is proportionate to the likelihood that a token is under a box of that color. The participant must guess whether a token is hidden inside a red or blue box and bet an amount of points on the choice. A winning choice is rewarded and a losing choice is deducted based on the number of points risked. For example, if the participant places a bet of 75 points and chooses red and the token is inside a red box, the participant will be awarded 75 points. However, if the participant chooses red and the token is inside a blue box, the participant loses 75 points. There are two conditions of the task, each with four trials (ascending and descending bet value). In the ascending condition, bets increase from 5% to 95% at 2.5 s intervals. In the descending condition, bets decrease from 95% to 5% at 2.5 s intervals. The CGT measures six aspects of performance: deliberation time, risk taking, delay aversion,

quality of decision-making, and risk adjustment. Deliberation time is the mean time (ms) from the presentation of boxes until a bet is selected. Risk taking measures the mean proportion of points bet on each trial when the more likely outcome is selected. Delay aversion is the difference between the amount of points risked in the descending condition v. the ascending condition. Quality of decision-making is calculated as the proportion of trials on which the participant chose to bet on the more likely outcome. Risk adjustment measures the extent to which a participant modulates their risk taking in response to the ratio of red to blue boxes (likelihood of success). In the CGT, there is always potential for losing a large percentage of acquired points in the face of a ratio, which appears to be a winning choice, and participants learn this on the practice trial. Therefore, even after learning the rules of the game, the participants need to modulate their behavior in the face of potential gain and loss. For example, they must consider whether they want to risk betting 95% of their points on a ratio with a high likelihood of success (9:1; 8:2), or whether a more balanced bet is wise considering potential loss. Thus, participants must maintain effective modulation of their decision-making behavior while being aware of potential reward and punishment. The ability to modulate behavior in the face of high and low potential for success is a task with an important emotion component (Bechara, 2004). Based on an *a priori* analysis plan and consistent with a prior study (Murphy et al., 2001), I constructed a decision-making score as standardized average of the two measures that specifically index hot decision-making: the quality of decision-making and risk adjustment.

2.3.8. Attention

Rapid Visual Information Processing (RVP (Sahakian, 1992))

We measured sustained attention using the rapid visual processing task from the CANTAB battery. Single digits appeared very briefly at the center of the screen (100 digits/min). Participants proceed through a practice trial which prompted them to identify the target sequence of three numbers (3-5-7, 2-4-6, 4-6-8). Following the practice trial, prompts were removed and participants were required to press a button when they were shown the target sequence. The Rapid Visual Information Processing task includes five primary outcome variables: 1) *RVP A'*: A measure of overall sensitivity to target. This variable represents overall "correct responding", and is calculated as 0.5+[(hits – false alarms) + (hits – false alarms)^2]/[4 x hits x (1 – false alarms)], 2) *RVP B"*: an overall measure of bias to make the 'yes' response (i.e., pressing the button regardless of whether target sequence is present), 3) probability of false alarm: 'false alarm' refers to pressing the button when viewing a sequence of numbers other than the target sequence 4) probability of hit: 'hit' refers to correctly responding when identifying the target sequence, 5) mean latency: mean time taken to respond. Based on an *a priori* data analysis plan, *RVP A'* was selected as the primary outcome variable for this task. This variable has also been selected as the primary variable of performance on the RVP task in previous research on offspring at familial risk for bipolar disorder and schizophrenia (Hemager et al., 2018).

2.4. Offspring clinical interview.

We assessed psychopathology among offspring aged 6-17 years with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL (Kaufman et al., 1997)). Participants aged 18-24 years were assessed with the Structured Clinical Interview for DSM-5 (SCID-5(First, 2015)). Diagnoses were

confirmed in consensus meetings with psychiatrists who were blind to parent psychopathology. In studies 1 and 2, diagnoses of ADHD and anxiety disorders were used in sensitivity analyses to account for these as potential confounding variables. In study 3, diagnoses of offspring new onset severe mental illness diagnoses were used as the primary dependent outcome variable.

2.5. Socioeconomic status

Socioeconomic status was assessed in interviews with parents and indexed by an ordinal variable constructed as a composite of five binary variables: (1) maternal and (2) paternal education beyond high school, (3) whether the family owns their primary residence, (4) household annual income above $60,000, and (5) family home having at least as many bedrooms as residents. The composite score ranged from 0 to 5, with a higher value indicating higher SES. Socioeconomic status was used in studies 1-3 in sensitivity analyses.

2.6. Cannabis use

We assessed cannabis use in semi-structured clinical interviews and validated substance use questionnaires. A composite variable was constructed, including any cannabis use reported on the Drug Use Screening Inventory (DUSI), and/or cannabis use or cannabis use disorder collected via the K-SADS or SCID clinical interview. Participants completed the DUSI questionnaire every 12 months and were asked to indicate how many times they had used cannabis in the past month. Ratings included 0 times, 1-2 times, 3-9 times, 10-20 times, more than 20 times. In analyses, we considered any ranking above 1 or more times on the DUSI or any reported cannabis use or any diagnosis of cannabis use disorder on the K-SADS or SCID clinical interview. Both self-

report (DUSI) and clinical interview (K-SADS or SCID) data were utilized in this variable because some participants were more comfortable reporting their cannabis use on the DUSI questionnaire and some were more comfortable reporting their use in clinical interviews with research assessors. Therefore, the range of values for this variable were binary (i.e., 0 = never used cannabis, 1 = used cannabis 1 or more times or meets criteria for cannabis use disorder). Cannabis use was used in sensitivity analyses to test the primary analysis. The cannabis use variable was employed in sensitivity analyses in study 2 and 3.

2.7. Parent Assessment

DSM-IV and DSM-5 diagnoses were established with the *Schedule for Affective Disorders and Schizophrenia* (SADS-IV (Endicott, 1978)) and the *Structured Clinical Interview for DSM 5 Disorders* (SCID-5 (First, 2015)). If a parent had more than one SMI diagnosis, primary mental disorder group was based on an established hierarchy of schizophrenia > bipolar disorder > major depressive disorder (Rasic et al., 2014). Demographic information was obtained from the parents, including physical health, family income, marital status, and education level of mother, father and/or relevant legal guardians.

2.8. Assessment of psychotic symptoms

Psychotic symptoms were defined as a definite psychotic symptom assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL), Funny Feelings instrument (FF), Schizophrenia Proneness

Instrument Child and Youth Version (SPI-CY), Structured Interview for Prodromal Syndromes (SIPS).

Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL). Interviewers blind to parent psychopathology assessed all youth and parents with K-SADS-PL (Kaufman, 1997) and established the presence of subclinical psychotic symptoms based on DSM-IV criteria and all available information in a consensus meeting with a child and adolescent psychiatrist, also blind to information on parent psychopathology. We used the K-SADS interview psychosis module and appendix to assess psychotic symptoms, which were also consensus rated by the child and adolescent psychiatrist blind to parent psychopathology. In analyses, we only considered psychotic symptoms coded as 'definite'.

Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003). In participants aged 11 and above, we also assessed psychotic symptoms with the SIPS, which allows the derivation of attenuated psychotic symptoms and definition of 'at risk mental state' for psychosis (Miller, 2003). In the analyses we only considered SIPS ratings at 3 and above that met clinical threshold for at risk mental state.

Funny Feelings (Arsenault, 2011).We also assessed self-reported psychotic symptoms with the 'Funny Feeling' interview where the self-reported answers to seven questions is corroborated with probes and independent clinical curation (Arsenault, 2011). We recorded frequency, distress, impairment and appraisal (internal/external, significant/not-significant) for each recent symptom. We submitted the verbatim transcript of each reported experience for independent clinical curation by psychologists and psychiatrists (blind to parent psychopathology) to establish a psychotic character of

experience, rated as none, probable or definite. In analyses, we only considered psychotic symptoms curated as definite by consensus between two independent raters.

Schizophrenia Proneness Instrument Child and Youth Version (SPI-CY) (Fux, Walger, Schimmelmann, & Schultze-Lutter, 2013). We interviewed participants aged 8 to 24 with the SPI-CY to assess basic symptoms. Basic symptoms are subjectively perceived deficits and abnormalities in multiple domains (perception, cognition, language, feelings) and often represent early manifestations of psychosis. Basic symptoms have been shown to strongly and specifically predict the development of schizophrenia (Klosterkotter, 2001). In analyses, we only considered basic symptoms fulfilling criteria for the high-risk profiles of cognitive disturbances (COGDIS) or cognitive-perceptive basic symptoms (COPER) that were shown to predict psychosis with high specificity (Schultze-Lutter, 2012).

2.10. Training meetings

During the period of data collection, I organized and hosted bi-weekly training meetings for all research staff in order to ensure ongoing data quality. On an ongoing basis, I invited psychologists to our meetings (via teleconference or in person) to provide additional training and consultation. I compiled minutes for each cognitive meeting, which were then added to the training manual for all research staff. In addition to the organization of training meetings for the cognitive data included in this thesis, I also provided training meetings for the assessment of psychotic symptoms in consultation with leading psychologists. In direct consultation with the author of the Schizophrenia Proneness Instument, Dr. Frauke Schultze-Lutter, I provided a full-day training workshop for all research staff in the assessment and scoring of psychotic symptoms using video

transcripts and scoring provided by Dr. Schultze-Lutter. Ongoing training meetings for the assessment of psychotic symptoms were held approximately every two to three months.

2.11. Double scoring

To ensure data fidelity, I trained a select group of research staff (all with prior training in the administration of cognitive tests) to double score all cognitive data for errors. I met with this core group on a monthly basis throughout the course of my PhD.

CHAPTER 3

Study 1: COGNITION IN OFFSPRING OF PARENTS WITH PSYCHOTIC AND NON-PSYCHOTIC SEVERE MENTAL ILLNESS

Contribution Statement

I drafted the manuscript, completed the data analysis, and devised the original idea for the chapter. I received guidance and editing from Dr. Rudolf Uher, Dr. Sherry Stewart, Dr. Kim Good, and the other co-authors. Data were collected by the FORBOW research team. I collected data and assisted with the ongoing training of the cognitive and clinical assessors.

3.1 Abstract

Background: Cognitive impairment is a feature of severe mental illness (SMI; schizophrenia, bipolar disorder, major depressive disorder). Psychotic forms of SMI may be associated with greater cognitive impairment, but it is unclear if this pre-dates illness onset or whether it reflects a consequence of disorder and treatment. To establish if there is a developmental impairment related to familial risk of psychotic SMI, I investigated cognition in offspring of parents with psychotic and non-psychotic SMI.

Method: Participants included 360 children and youth (mean age 11.10, SD 4.03, range 6 to 24), including 68 offspring of parents with psychotic SMI, 193 offspring of parents with non-psychotic SMI, and 99 offspring of control parents. The cognitive battery was designed to assess a range of functions using standardized cognitive tests and executive function tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB).

Results: Compared to controls, offspring of parents with psychotic SMI performed significantly worse on overall cognition ($\beta = -0.32$; $p < 0.001$) and 6 of 15 cognitive domains, including verbal intelligence ($\beta = -0.48$; $p = 0.005$), verbal working memory ($\beta = -0.62$; $p < 0.001$), processing speed ($\beta = -0.37$; $p = 0.047$), verbal learning and memory ($\beta = -0.54$; $p = 0.003$), verbal fluency ($\beta = -0.37$; $p = 0.045$), and sustained attention ($\beta = -0.59$; $p = 0.006$). Offspring of parents with non-psychotic SMI performed significantly worse than controls on 3 of the 15 domain specific cognitive tests, including verbal

intelligence (β = -0.28; p = 0.041), visual memory (β = -0.34; p = 0.041) and decision-making (β = -0.24; p = 0.017).

Conclusions: Mild cognitive impairment may be a marker of transdiagnostic familial liability for any form of SMI. Additional impairments in verbal cognition, verbal memory, verbal fluency, processing speed and sustained attention may be markers of familial liability for psychotic SMI.

Key words: Schizophrenia, bipolar disorder, major depressive disorder, transdiagnostic, severe mental illness, psychotic symptoms, offspring, verbal working memory, verbal learning, spatial working memory, processing speed, sustained attention, cognition.

3.2 Introduction

Severe mental illness (SMI) includes schizophrenia (and psychotic disorders), bipolar disorder, and major depressive disorder. SMI affects 5-10% of the population (Kessler, Berglund, Bruce, 2001; *U.S. Census Bureau. 2010 Resident Population*, 2010) onsets early in life, and causes significant impairment in lifelong functioning (Drake & Whitely, 2014). Psychotic symptoms occur transdiagnostically among individuals with SMI (Hanssen, 2003; Keck, 2003; Olfson, 2002). Additionally, cognitive impairment (McTeague, Goodkind, & Etkin, 2016) is a common feature that is shared across the transdiagnostic range of SMI. Cognitive ability is a strong predictor of long-term functional outcomes in patients with SMI (Green, 1996). Psychotic SMI has been associated with greater cognitive impairment compared to non-psychotic SMI (Brasso & Bornstein, 1999; Jimenez-Lopez et al., 2017; Lee et al., 2013; Maziade et al., 2011; McCarthy et al., 2016; Trisha et al., 2018; Zaninotto et al., 2015). However, it is unclear whether the worse cognitive performance in people with psychotic mental illness is a consequence of disease burden or is a pre-existing neurodevelopmental risk factor.

It is possible to distinguish developmental cognitive impairments associated with familial liability to SMI from the consequences of illness and its treatment by examining cognition among the unaffected offspring of affected parents. Offspring of parents with schizophrenia and bipolar disorder have shown lower cognitive performance compared to control offspring (Bora, 2017; de la Serna et al., 2017). However, it is unclear whether sons and daughters of parents with transdiagnostic psychotic SMI perform worse than offspring of parents with non-psychotic illness. Offspring of parents with SMI are at greater than 2-fold increased risk of developing SMI themselves by early adulthood

(Rasic et al., 2014). Several prospective studies suggest that mild cognitive impairment may be an indicator of neurodevelopmental risk that is present before SMI onset, and is present among unaffected relatives of individuals with SMI (Keshavan et al., 2010; Koenen et al., 2009; Scult et al., 2017). In contrast, other studies raise the possibility that cognitive impairment may be a consequence of disease burden, its comorbidities or its treatment (Moraros et al., 2017; Schaefer et al., 2017). It is important to characterize the cognitive profile of individuals at familial risk for psychotic and non-psychotic SMI to better understand the etiological mechanisms underlying SMI development.

Thus far, investigation of cognition in individuals at familial high risk for SMI has been largely disorder-specific and has not been examined transdiagnostically across major mood and psychotic disorders (Bora, 2017; Bora et al., 2009; Gur, 2007; Snitz et al., 2006). However, current models support a significant degree of overlap between genetic, clinical and cognitive characteristics for the spectrum of SMI and psychotic illness (Cuthbert & Insel, 2010). The present study seeks to investigate the relationships between transdiagnostic psychotic and non-psychotic parental SMI and offspring cognitive function. We assessed cognition with standardized paper-and-pencil tests and computerized tests from the Cambridge Automated Neuropsychological Test Battery (CANTAB). In Study 1, we hypothesized that offspring of parents with any form of SMI would show mild cognitive impairment compared to control offspring with no family history of SMI. Based on previous literature, we additionally hypothesized that offspring of parents with transdiagnostic psychotic SMI would show more widespread cognitive impairments than offspring of parents with non-psychotic SMI.

3.3 Methods

3.3.1. Sample description

The sample is composed of 360 participants aged 6-24 years, recruited as part of the ongoing cohort, *Families Overcoming Risks and Building Opportunities for Well-being* (FORBOW) study. FORBOW is an accelerated cohort study enriched for family history of SMI. Offspring of parents with SMI were recruited through parent's contact with adult mental health services in Nova Scotia, Canada.

Additional inclusion criteria for the present study were (1) age between 6 and 24 years (the age range for which most cognitive tests are validated and normed), and (2) English as a primary language spoken in the home. Exclusion criteria were (1) serious brain injury resulting in inability to complete cognitive testing or (2) Full-scale IQ <70 or intellectual disability of a degree that would invalidate assessment. Ethical approval of the study was granted through the Research Ethics Board of the Nova Scotia Health Authority. All participants with capacity provided written informed consent. For children who did not have capacity to make an informed choice, a parent or legal guardian provided written informed consent and the child provided assent.

3.3.2. Parent Assessment

Parent assessments were administered by research staff separate from those who assessed offspring. Parent assessors were blinded to child psychopathology and vice versa for offspring assessors. Lifetime DSM-IV and DSM-5 diagnoses and presence of psychotic symptoms were established with the *Schedule for Affective Disorders and Schizophrenia* (SADS-IV (Endicott & Spitzer, 1978)) and the *Structured Clinical Interview for DSM 5 Disorders* (SCID-5 (First, Williams & Spitzer, 2015)). Lifetime

diagnoses of mental disorders were confirmed in consensus meetings with psychologists and psychiatrists.

3.3.3 Offspring Assessment

3.3.3.1 Clinical Interview

We assessed psychopathology among offspring aged 6-17 years with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL (Kaufman et al., 1997)). Participants aged 18-24 years were assessed with the Structured Clinical Interview for DSM-5 (SCID-5). Diagnoses were confirmed in consensus meetings with psychiatrists who were blind to parent psychopathology.

3.3.3.2 Cognition

The cognitive battery was designed to assess a range of cognitive function using standardized paper-and-pencil neuropsychological tests and computerized tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB) (Sahakian, 1992). We assessed general cognitive ability with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). We assessed verbal learning and memory with the California Verbal Learning Test, Children's Version (CVLT-C) (Delis et al., 1994) (among participants aged 6-15 years) and the California Verbal Learning Test, Second Edition (CVLT-II;(Delis, 2000) (among participants aged 16-24 years). We assessed story memory using the Children's Memory Scale (CMS; (Cohen, 1997) (among participants aged 6-15 years) and the Wechsler Memory Scale (WMS) (Wechsler, 1997) (among participants aged 16-24 years). We assessed visual memory among participants aged 8-24 years using the Benton Visual Retention Test (Benton, 1974). We assessed processing speed with the Digit Symbol Coding subtest of the WISC-IV (among

participants aged 6-15 years) and the WAIS-IV (among participants aged 16-24 years) (Wechsler, 2003, 2008). We measured cold executive function (or emotion-independent executive function) using the following tasks: (1) verbal working memory using the Letter Number Sequencing subtest of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; participants aged 6-15 years) and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; participants aged 16-24 years) (2) verbal fluency with the Letter Fluency subtest of the Delis Kaplan Executive Functioning System (Delis et al., 2001b) (among participants aged 8-24 years), (3) visual working memory using the Spatial Working Memory subtest from the CANTAB battery (among participants aged 7-24 years), (4) response inhibition using the Stop Signal Task of the CANTAB (among participants aged 6-24 years). We measured hot or emotion-laden executive function using the Cambridge Gambling Task from the CANTAB battery (among participants aged 7-24 years). One primary variable from each task was selected *a priori* as the best estimate of overall performance on each task. Full details of the cognitive battery are listed in Chapter 2 of this thesis.

3.3.3.3 Socioeconomic status

Socioeconomic status was assessed in interviews with parents and indexed by an ordinal variable constructed as a composite of five binary variables: (1) maternal and (2) paternal education beyond high school, (3) whether the family owns their primary residence, (4) household annual income above $60,000, and (5) family home having at least as many bedrooms as residents. The composite score ranged from 0 to 5, with a higher value indicating higher SES. Socioeconomic status was used in sensitivity analyses.

3.3.4 Data Analysis

In the present study, only the participant's first completion of each cognitive measure was analyzed. There were no repeated assessments included in this analysis. Dependent variables were continuous measures of performance on cognitive tasks, standardized to participant's age and sex. The primary independent variables were parent history of (1) psychotic and (2) non-psychotic SMI; these were binary variables, where 0 = no lifetime history of SMI, and 1= lifetime history of SMI diagnosis. Cognitive variables were z-score standardized to a control group (mean of 0 and standard deviation of 1) and coded so that lower scores indicate worse performance (error variables were inverted). To account for non-independence of observations from related individuals (siblings), we tested the relationship between parent SMI and performance on cognitive tasks using mixed effects linear models implemented in STATA 15.1. We included the family identifier as a random effect in the models. We first performed a single test of overall cognitive ability, constructed as a composite variable averaging across all 15 cognitive tests. The overall cognition score and FSIQ score were strongly correlated (r = 0.79), therefore the FSIQ score was omitted from further analyses. Then we proceeded to complete domain-specific analyses testing each of the 15 cognitive measures. For domain-specific analyses we report both nominal significance ($p < 0.05$) and Bonferroni corrected p-values accounting for 15 tests ($p < 0.003$). Associations with p-value less than 0.05 were considered nominally statistically significant. Associations with p-value less than 0.003 were considered statistically significant after correcting for multiple comparisons. The primary aim of this study was to analyze differences in cognitive performance of offspring of parents with non-psychotic and psychotic SMI compared

with control offspring. We conducted sensitivity analyses to probe whether the results were independent of socioeconomic status and offspring diagnoses of attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders. The secondary analyses within this chapter include a separate analysis of overall cognition and the 15 domain-specific cognitive tests analyzed by parent diagnostic group (e.g., offspring of parents affected with Major Depressive Disorder with psychotic and non-psychotic features, offspring of parents with Bipolar Disorder with psychotic and non-psychotic features, and offspring of parents with Schizophrenia and Psychotic Disorders) compared with control offspring. Effect sizes are reported as standardized regression estimates with 95% confidence intervals (95% CI). We completed pairwise correlations between all cognitive tests (Table 3.1).

3.3.5 Missing Data

Analysis of missing data was completed on each of the cognitive tests (Table 3.2). The two major sources of missing data were the age range for which tests were validated (i.e., Benton Visual Retention Test, Delis Kaplan Executive Function System, Cambridge Gambling Task, Spatial Working Memory, Intra/Extra Dimensional Set Shifting, Rapid Visual Processing, Stop Signal Task; see Table 2.1 in Chapter 2) and delayed addition of several CANTAB tests due to the longitudinal design of the FORBOW study, and the effort to minimize burden of lengthy cognitive protocols (e.g., maximum cognitive assessment length 2-2.5 hours including breaks; see Chapter 2 for additional information regarding protocol design). Otherwise, there was no systematic pattern of missing data across the 360 offspring.

Table 3.1. Correlations between cognitive tasks

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Overall Cognition	1																
2. FSIQ	0.79	1															
3. Block Design	0.54	0.58	1														
4. Matrix Reasoning	0.61	0.61	0.45	1													
5. Vocabulary	0.75	0.69	0.33	0.40	1												
6. Similarities	0.65	0.64	0.31	0.39	0.61	1											
7. LNS	0.63	0.44	0.28	0.39	0.33	0.30	1										
8. Coding	0.57	0.33	0.21	0.16	0.23	0.26	0.39	1									
9. CVLT	0.57	0.37	0.16	0.24	0.28	0.30	0.33	0.38	1								
10. Story Memory	0.51	0.31	0.05	0.11	0.31	0.32	0.22	0.19	0.35	1							
11. Verbal Fluency	0.49	0.32	0.12	0.15	0.25	0.28	0.19	0.33	0.38	0.21	1						
12. BVRT	0.55	0.45	0.36	0.31	0.28	0.26	0.27	0.18	0.16	0.13	0.14	1					
13. CGT	0.47	0.26	0.14	0.15	0.16	0.16	0.14	0.19	0.08	0.11	0.07	0.30	1				
14. SWM	0.53	0.32	0.20	0.21	0.10	0.13	0.22	0.20	0.22	0.19	0.16	0.36	0.40	1			
15. IED	0.49	0.26	0.24	0.14	0.13	0.16	0.18	0.09	0.07	0.17	0.09	0.28	0.20	0.29	1		
16.SST	0.19	0.06	0.08	0.09	-0.01	0.00	0.07	-0.04	0.09	-0.01	0.15	0.17	0.07	0.19	0.15	1	
17. RVP	0.49	0.25	0.12	0.19	0.17	0.17	0.23	0.25	0.18	0.18	0.14	-0.00	0.14	0.02	0.16	-0.09	1

Note. **N=360.** FSIQ = Full Scale Intelligence Quotient, LNS = Letter Number Sequencing, Coding = Digit Symbol Coding, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, CGT = Cambridge Gambling Task, SWM=Spatial Working Memory, IED = Intra/Extra Dimensional Set Shifting, SST = Stop Signal Task, RVP = Rapid Visual Processing Task.

Table 3.2. Cognitive tests by age range and data completeness for cognitive domains

Cognitive Domain	Sub-domain	Cognitive Test	Age Range	Sample (N)	Percentage of missing data
General Intelligence	FSIQ	WASI (4 subtest version)	6-24	360	0%
	Vocabulary	WASI	6-24	360	0%
	Similarities	WASI		360	0%
	Block Design	WASI	6-24	360	0%
	Matrix Reasoning	WASI	6-24	360	0%
Memory	Verbal story memory	Story Memory; Children's Memory Scale; Wechsler Memory Scale	6-15; 16-24	284	21.11%
	Verbal learning and memory	CVLT	6-24	315	12.50%
	Visual Memory	BVRT	8-24	186	48.33%
Executive Function	Set Shifting	Intra-Extra Dimensional	7-24	178	50.56%
	Verbal fluency	DKEFS Verbal Fluency	8-24	272	24.44%
	Decision-making	Cambridge Gambling Task	8-24	308	14.44%
	Verbal working memory	Letter number sequencing WISC/WAIS	6-15; 16-24	300	16.67%
	Visual working memory	Spatial Working Memory	7-24	339	5.83%
	Response Inhibition	Signal Stop Task	6-24	199	44.72%
Processing speed		Digit Symbol Coding WISC/WAIS	6-15; 16-24	268	25.55%
Attention	Sustained attention	Rapid Visual Information Processing	6-24	228	36.67%

Note. **N=360.** FSIQ = Full Scale Intelligence Quotient, WASI = Wechsler Abbreviated Scale of Intelligence, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, WAIS = Wechsler Adult Intelligence Scale, WISC = Wechsler Intelligence Scale for Children, DKEFS = Delis Kaplan Executive Function System

3.4 Results

3.4.1. Sample characteristics

Of the 360 participants aged 6 to 24, 193 (53.61%) had at least one parent who had a lifetime history of non-psychotic SMI, 68 (18.89%) had at least one parent who had a lifetime history of psychotic SMI, and 99 (27.50%) had no lifetime family history of SMI in either parent. **Table 3.3** presents demographic and descriptive characteristics of the participants.

3.4.2. Relationship between measures of cognitive ability

The cognitive domains were moderately to strongly correlated with one another (r = 0.31 to 0.61). The overall cognition score and FSIQ score were strongly correlated, therefore the FSIQ score was omitted from further analyses. No additional correlation reached the recommended cut-off for omitting strongly correlated variables (Vatcheva, Lee, McCormick, & Rahbar, 2016); therefore, all 15 measures were included in further analyses. **Table 3.1** presents bivariate correlations between all cognitive tests.

Table 3.3. Demographic characteristics for offspring of parents with non-psychotic and psychotic severe mental illness

	Control	**Parent Non-Psychotic SMI**	**Parent Psychotic SMI**
	(n=99)	**(n=193)**	**(n= 68)**
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Age (years)	10.63 (3.41)	11.48 (4.30)	10.73 (4.03)
Socioeconomic status	3.48 (1.11)	2.97 (1.35)	2.66 (1.41)
	Count (%)	Count (%)	Count (%)
Sex (Male/Female)	56 (56.57)/ 43 (43.43)	98 (50.78)/ 95 (49.22)	25 (36.76)/ 43 (63.24)
Offspring Diagnoses			
ADHD, n (%)	9 (9.09)	36 (18.65)	13 (19.12)
Anxiety, n (%)	23 (23.23)	75 (39.06)	23 (33.82)
Parent Diagnoses			
Control	0	0	0
MDD, n (%)	0	142 (73.58)	16 (23.53)
BD, n (%)	0	51 (26.42)	33 (48.53)
SCH, n (%)	0	0	19 (27.94)

Note. **N=360.** No SMI = No family history of severe mental illness, SMI = Offspring of parent affected with severe mental illness, Psychotic SMI = Offspring of parent affected with transdiagnostic severe mental illness, SES = Socioeconomic status, ADHD = Attention Deficit Hyperactivity Disorder, Anxiety = Any anxiety disorder, MDD = Major Depressive Disorder, BD = Bipolar Disorder, SCH = Schizophrenia.

3.4.3 Association of parent psychotic and non-psychotic SMI and overall cognitive performance

Compared to controls, offspring of parents with psychotic SMI performed significantly worse on the composite measure of overall cognition (β = -0.32, 95% CI -0.50 to -0.15, $p = 0.000$). Offspring of parents with non-psychotic SMI did not differ significantly from controls on overall cognition (β = -0.12, 95% CI -0.26 to 0.01, $p = 0.089$) (**Table 3.4**).

In sensitivity analyses, the association between parent diagnosis of psychotic SMI and offspring overall cognition remained significant after controlling for socioeconomic status, and offspring lifetime diagnoses of ADHD and any anxiety disorder. Full details from sensitivity analyses are listed in **Table 3.5**.

3.4.4 Association of parent history of psychotic SMI and offspring cognitive performance

Compared to controls, offspring of parents with psychotic SMI performed significantly worse in 3 of the 15 cognitive tests, including Letter Number Sequencing (β = -0.62, 95% CI -0.95 to -0.28, $p < 0.001$), California Verbal Learning Test (β = -0.54, 95% CI -0.89 to -0.18, $p = 0.003$). Only Letter Number Sequencing and California verbal learning test were significant after Bonferroni correction. Offspring of parents with psychotic SMI performed nominally worse on 4 of the 15 cognitive tests, including vocabulary (β = -0.48, 95% CI -0.82 to -0.15, $p = 0.005$), verbal fluency (β = -0.37, 95% CI -0.73 to -0.01, $p = 0.045$), digit symbol coding (β = -0.37, 95% CI -0.74 to -0.01, $p = 0.047$), and the rapid visual processing (β = -0.59, 95% CI -1.00 to -0.17, $p = 0.006$) **(Table 3.4; Figure 3.1)**.

Table 3.4. *Differences from control offspring in cognitive performance of offspring of parents with non-psychotic and psychotic severe mental illness*

	Non- Psychotic SMI					Parent Psychotic SMI				
Cognitive Test	Beta	SE	p	95% CI Lower	95% CI Upper	Beta	SE	p	95% CI Lower	95% CI Upper
Overall Cognition	-0.12	0.07	0.089	-0.26	0.01	-0.32	0.09	0.000	-0.50	-0.15
Block Design	-0.08	0.13	0.569	-0.34	0.18	-0.32	0.17	0.063	-0.65	0.02
Matrix Reasoning	-0.03	0.13	0.802	-0.29	0.22	-0.29	0.17	0.078	-0.62	0.03
Vocabulary	-0.28	0.13	0.041	-0.54	-0.01	-0.48	0.17	0.005	-0.82	-0.15
Similarities	-0.10	0.13	0.443	-0.35	0.15	-0.27	0.16	0.103	-0.59	0.05
LNS	-0.11	0.13	0.384	-0.36	0.14	-0.62	0.17	0.000	-0.95	-0.28
Coding	-0.11	0.14	0.450	-0.39	0.17	-0.37	0.19	0.047	-0.74	-0.01
CVLT	-0.10	0.14	0.460	-0.38	0.17	-0.54	0.18	0.003	-0.89	-0.18
Story Memory	0.00	0.15	0.979	-0.28	0.29	-0.35	0.19	0.061	-0.72	0.02
Verbal Fluency	-0.24	0.14	0.084	-0.51	0.03	-0.37	0.19	0.045	-0.73	-0.01
BVRT	-0.34	0.17	0.041	-0.67	-0.01	-0.30	0.21	0.144	-0.71	0.10
CGT	-0.24	0.10	0.017	-0.43	-0.04	-0.26	0.13	0.052	-0.51	0.00
SWM	-0.21	0.12	0.077	-0.45	0.02	-0.14	0.16	0.373	-0.45	0.17
IED	-0.06	0.21	0.787	-0.48	0.36	-0.10	0.24	0.680	-0.57	0.37
SST	-0.04	0.09	0.638	-0.22	0.13	-0.18	0.12	0.114	-0.41	0.04
RVP	-0.31	0.18	0.091	-0.66	0.05	-0.59	0.21	0.006	-1.00	-0.17

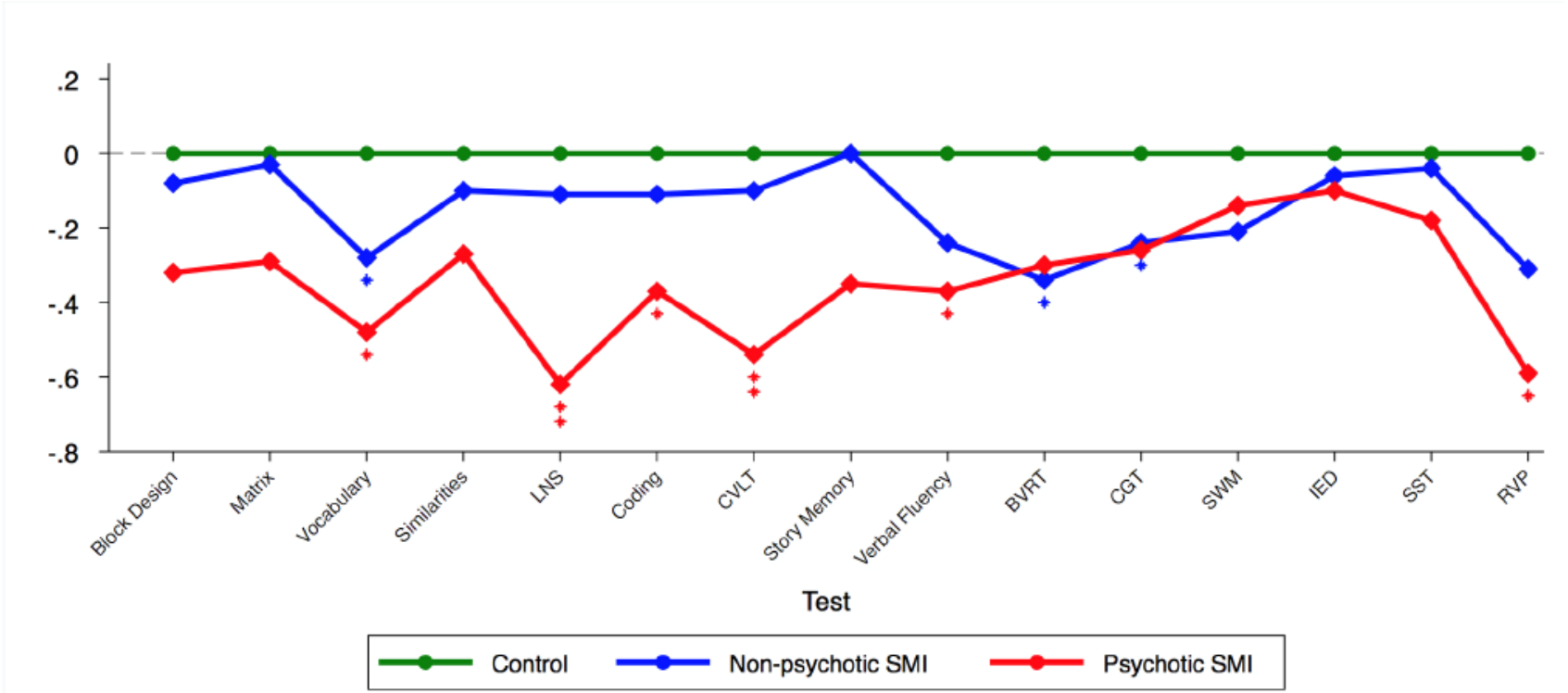
Note. **N=360.** Parent SMI = Offspring of parents with SMI, Parent Psychotic SMI = Offspring of parents with psychotic SMI, SE = Standard Error, 95% CI = 95% confidence interval, FSIQ = Full Scale Intelligence Quotient, LNS = Letter Number Sequencing, Coding = Digit Symbol Coding, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, CGT = Cambridge Gambling Task, SWM=Spatial working memory, IED = Intra/Extra Dimensional Set Shifting, SST=Signal Stop Task, RVP = Rapid Visual Processing.

Table 3.5. *Sensitivity analyses probing effect of sample characteristics on overall cognitive performance in offspring of parents with psychotic SMI*

	Parent psychotic SMI				
Sensitivity Analysis	Beta	SE	p-value	95% CI Lower	95% CI Upper
SES	-0.22	0.09	0.010	-0.39	-0.05
ADHD	-0.28	0.08	0.001	-0.45	-0.12
Anxiety Disorders	-0.32	0.09	<0.001	-0.49	-0.16

Note. **N = 360.** Parent Psychotic SMI = Offspring of parents with psychotic SMI, SE = Standard Error, 95% CI = 95% confidence interval, SES = Socioeconomic status, ADHD = Attention Deficit Hyperactivity Disorder.

Fig. 3.1. *Performance on cognitive tests by individuals with familial risk for non-psychotic and psychotic severe mental illness*



Note. **N=360.** Measures of performance are z-scored (control group mean 0, standard deviation 1). One diamond indicates p<.05, two stars indicates p<.003. Matrix = Matrix Reasoning, LNS = Letter Number Sequencing, Coding = Digit Symbol Coding, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, CGT = Cambridge Gambling Task, SWM=Spatial working memory, IED = Intra/Extra Dimensional Set Shifting, SST = Signal Stop Task, RVP = Rapid Visual Processing.

3.4.5 Association of parent history of non-psychotic SMI and offspring domain specific cognitive performance

None of the domain-specific differences were significant after correction for multiple testing. Compared to controls, offspring of parents with non-psychotic SMI performed nominally worse on 3 of the 15 cognitive tests, including Vocabulary (β = -0.28, 95% CI -0.54 to -0.01, $p = 0.041$), Benton Visual Retention Test (β = -0.34, 95% CI -0.67 to -0.01, $p = 0.041$), and Cambridge Gambling Task (β = -0.24, 95% CI -0.43 to -0.04, $p = 0.017$) **(Table 3.4; Figure 3.1)**.

3.4.6 Post-hoc comparison of overall cognitive performance between psychotic and non-psychotic SMI

Offspring of parents performed significantly worse on overall cognitive performance compared to offspring of parents with non-psychotic SMI (β = -0.20, 95% CI -0.39 to -0.01, $p = 0.038$).

3.4.7 Association of parent diagnosis of major depressive disorder and offspring cognitive performance

Offspring of parents with major depressive disorder (psychotic and non-psychotic features included) did not differ significantly from controls on overall cognition (β = -0.07, 95% CI -0.21 to 0.07, $p = 0.359$). Compared to controls, offspring of parents with major depressive disorder performed nominally worse on 2 of the 15 cognitive tests, including verbal fluency (β = -0.29, 95% CI -0.57 to -0.01, $p = 0.046$), and the Cambridge

Gambling Task (β = -0.23, -0.44 to -0.03, p = 0.027) (**Table 3.6 and Figure 3.2**). None of the domain-specific differences were significant after Bonferroni correction.

3.4.8 Association of parent diagnosis of bipolar disorder and offspring cognitive performance

Compared to controls, offspring of parents with bipolar disorder (psychotic and non-psychotic features included) performed nominally worse than controls on the composite measure of overall cognition (β = -0.18, 95% CI -0.35 to -0.02, p =0.031). This association was not significant after Bonferroni correction. Compared to controls, offspring of parents with bipolar disorder performed significantly worse in Vocabulary (β = -0.56, 95% CI -0.87 to -0.24, p = 0.001), and Rapid Visual Processing (β = -0.80, 95% CI -1.22 to -0.38, p = <0.001). Offspring of parents with bipolar disorder performed nominally worse than controls on Similarities (β = -0.32, 95% CI -0.62 to -0.02, p = 0.034), California Verbal Learning Test (β = -0.34, 95% CI -0.68 to -0.01, p = 0.047), and the Cambridge Gambling Task (β = -0.27, 95% CI -0.51 to -0.04, p = 0.023) (**Table 3.6 and Figure 3.2**). We found no difference between offspring of parents with bipolar disorder compared with controls on Block Design, Matrix Reasoning, Letter Number Sequencing, Digit Symbol Coding, Story Memory, Verbal Fluency, Spatial Working Memory, Intra/Extra Dimensional Set Shifting, and the Signal Stop Task.

3.4.9 Association of parent diagnosis of schizophrenia and offspring cognitive performance

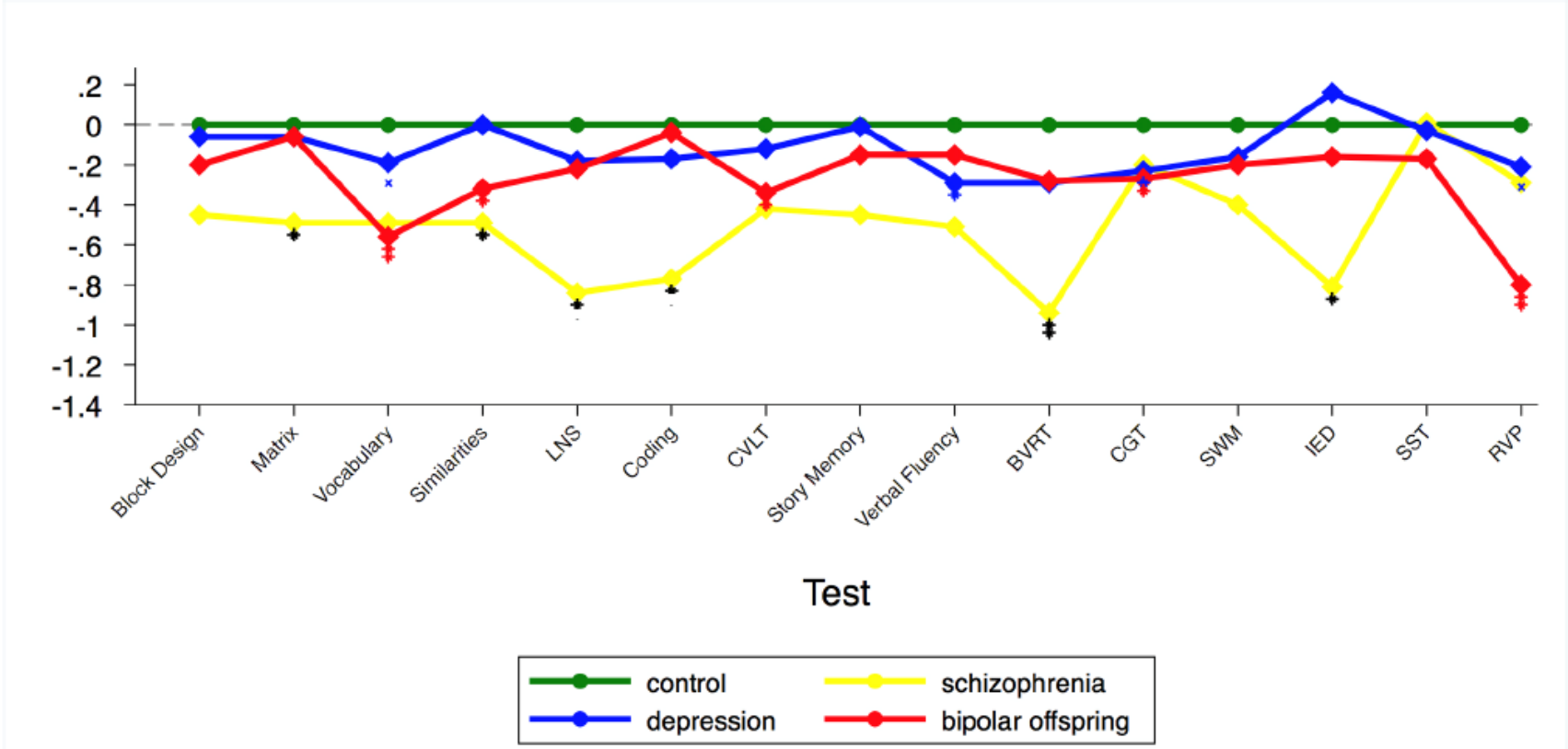
Offspring of parents affected with schizophrenia performed significantly worse than controls on a composite measure of overall cognition (β = -0.41, 95% CI -0.65 to -0.17, p = 0.001). Compared to controls, offspring of parents with schizophrenia performed significantly worse on the Benton Visual Retention Test (β = -0.94, 95% CI -1.55 to -0.33, p = 0.003). After Bonferroni correction, no other cognitive test significantly differed between offspring of parents with schizophrenia relative to controls. Compared with controls, offspring of parents with schizophrenia performed nominally worse than controls on Matrix Reasoning (β = -0.49, 95% CI -0.98 to -0.01, p = 0.048), Similarities (β = -0.49, 95% CI -0.97 to -0.01, p = 0.049), Letter Number Sequencing (β = -0.84, 95% CI -1.42 to -0.26, p = 0.004), Digit Symbol Coding (β = -0.77, 95% CI -1.35 to -0.19, p = 0.009), and Intra/Extra Dimensional Set Shifting (β = -0.81, 95% CI -1.47 to -0.15, p = 0.016) (**Table 3.6 and Figure 3.2**). We found no difference between offspring of parents with schizophrenia and controls in Block Design, Vocabulary, California Verbal Learning Test, Story Memory, Verbal Fluency, Cambridge Gambling Task, Spatial Working Memory, Signal Stop Task, and the Rapid Visual Processing Task.

Table 3.6. *Differences from control offspring in cognitive performance of offspring of parents with Major Depressive Disorder, Bipolar Disorder and Schizophrenia*

	MDD N=158				BD N=84				SCH N=19			
Cognitive Test	Beta	p value	95% CI Lower	95% CI Upper	Beta	p value	95% CI Lower	95% CI Upper	Beta	p value	95% CI Lower	95% CI Upper
Overall Cognition	-0.07	0.359	-0.21	0.07	-0.18	0.031	-0.35	-0.02	-0.41	0.001	-0.65	-0.17
Block Design	-0.06	0.676	-0.33	0.21	-0.20	0.225	-0.51	0.12	-0.45	0.069	-0.94	0.03
Matrix Reasoning	-0.06	0.671	-0.32	0.21	-0.06	0.681	-0.37	0.24	-0.49	0.048	-0.98	-0.01
Vocabulary	-0.19	0.174	-0.5	0.08	-0.56	0.001	-0.87	-0.24	-0.49	0.053	-0.98	0.01
Similarities	0.00	0.989	-0.26	0.26	-0.32	0.034	-0.62	-0.02	-0.49	0.049	-0.97	-0.01
LNS	-0.18	0.176	-0.45	0.08	-0.22	0.189	-0.55	0.11	-0.84	0.004	-1.42	-0.26
Coding	-0.17	0.255	-0.45	0.12	-0.04	0.831	-0.38	0.30	-0.77	0.009	-1.35	-0.19
CVLT	-0.12	0.428	-0.4	0.17	-0.34	0.047	-0.68	-0.01	-0.42	0.148	-0.99	0.15
Story Memory	-0.01	0.962	-0.31	0.30	-0.15	0.413	-0.49	0.20	-0.45	0.125	-1.02	0.12
Verbal Fluency	-0.29	0.046	-0.57	-0.01	-0.15	0.372	-0.49	0.18	-0.51	0.067	-1.06	0.04
BVRT	-0.29	0.098	-0.62	0.05	-0.28	0.146	-0.66	0.10	-0.94	0.003	-1.55	-0.33
CGT	-0.23	0.027	-0.44	-0.03	-0.27	0.023	-0.51	-0.04	-0.20	0.353	-0.62	0.22
SWM	-0.16	0.192	-0.41	0.08	-0.20	0.183	-0.48	0.09	-0.40	0.096	-0.86	0.07
IED	0.16	0.461	-0.26	0.58	-0.16	0.467	-0.60	0.27	-0.81	0.016	-1.47	-0.15
SST	-0.03	0.745	-0.21	0.15	-0.17	0.102	-0.38	0.03	0.01	0.971	-0.39	0.41
RVP	-0.21	0.243	-0.57	0.14	-0.80	<0.001	-1.22	-0.38	-0.29	0.279	-0.83	0.24

Note. N=360. MDD = Major Depressive Disorder, BD = Bipolar Disorder, SCH = Schizophrenia, SE = Standard Error, 95% CI = 95% confidence interval, Overall = overall cognition, FSIQ = Full Scale Intelligence Quotient, LNS = Letter Number Sequencing, Coding = Digit Symbol Coding, CVLT = California Verbal Learning Test, Story = Story Memory, BVRT = Benton Visual Retention Test, CGT = Cambridge Gambling Task, SWM=Spatial working memory, IED = Intra/Extra Dimensional Set Shifting, SST = Stop Signal Task, RVP = Rapid Visual Processing.

Fig. 3.2. *Performance on cognitive tests by individuals with familial risk for major depressive disorder, bipolar disorder and schizophrenia compared with controls*



Note. **N=360.** LNS = Letter Number Sequencing, Coding = Digit Symbol Coding, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, CGT = Cambridge Gambling Task, SWM = Spatial Working Memory, IED = Intra/Extra Dimensional Set Shifting, SST = Stop Signal Task, RVP = Rapid Visual Processing. One diamond indicates p<.05, two stars indicates p<.003.

3.5. Discussion

The present study shows that lower cognitive ability is a feature of familial liability to SMI, rather than an effect of disease and treatment burden. Compared to controls, sons and daughters of parents affected with non-psychotic SMI performed nominally worse on verbal intelligence, visual memory, and decision-making. However, none of the findings remained significant after correction for multiple comparison. Sons and daughters of parents affected with psychotic SMI showed significant impairments in overall cognition, verbal working memory, and verbal learning and memory compared to offspring of control parents. Offspring of parents with psychotic SMI performed nominally worse than controls on processing speed, verbal fluency and sustained attention. The relationship between parent psychotic SMI and offspring cognition was independent of socioeconomic status and attention deficit/hyperactivity disorder and anxiety disorders in the offspring.

Our results are consistent with previous findings of lower cognitive ability in individuals at familial high risk for schizophrenia compared to those at familial risk for mood disorders. In the largest familial high risk cohort to date that investigated the association between parent diagnoses of schizophrenia and bipolar disorder and offspring cognitive ability, Hemager et al. (2018) found widespread cognitive impairments in 7-year old offspring of parents with schizophrenia, and no impairment in same aged children of parents with bipolar disorder. Similarly, the present study found no significant difference in overall cognitive performance between offspring of parents at familial risk for non-psychotic SMI compared with controls, and significantly worse overall cognitive performance in offspring of parents with psychotic SMI compared with controls. Our

results extend previous findings to indicate that nominally worse cognitive ability in verbal cognition, visual memory, and decision-making is also present later in development for offspring at familial risk for non-psychotic SMI compared with controls.

3.5.1 Shared impairments in offspring of parents with psychotic and non-psychotic SMI

Offspring of parents with psychotic and non-psychotic SMI showed mild-to-moderate impairment in verbal IQ subtests. This is in line with findings of verbal cognition impairments across meta-analyses of individuals at risk for major depressive disorder (MacKenzie et al., 2018), bipolar disorder (Arts, Jabben, Krabbendam & van Os, 2007; Bora et al., 2009; Bora & Ozerdem, 2017), and psychotic disorders (Bora, 2017). Shared impairment in verbal cognition is inconsistent with a recent study comparing offspring at familial risk for bipolar disorder and schizophrenia (de la Serna et al., 2017). However, the transdiagnostic approach to group comparison, larger sample size, and addition of severe major depressive disorder and major depressive disorder with psychotic features may account for the different findings within this thesis.

3.6.2. Segregating impairments between offspring of parents with psychotic and non-psychotic SMI

Offspring of parents with non-psychotic SMI performed nominally worse than controls within the domains of visual memory and decision-making, yet these domains remained intact in offspring of parents with psychotic SMI. This is in line with previous meta-analytic findings of visual memory impairment in youth at familial risk for bipolar disorder (Bora & Ozerdem, 2017). It is notable that none of the fifty-four independent

samples in our recent meta-analysis of cognitive performance in first-degree relatives of major depressive disorder assessed visual memory (MacKenzie et al., 2018). Our results indicate that visual memory impairment may be specifically impaired in individuals at familial risk for nonpsychotic SMI. Additional research comparing offspring of parents affected with psychotic and nonpsychotic SMI within this cognitive domain is needed. Two of the fifty-four samples in the aforementioned meta-analysis of cognitive performance in first-degree relatives of major depressive disorder assessed decision-making ability (Hoehne, Richard-Devantoy, Ding, Turecki, & Jollant, 2015; Mannie, Williams, Browning, & Cowen, 2015). Mannie et al. (2015) found that young people at familial risk for depression have lower risk taking behaviour on the Cambridge Gambling Task compared with controls. Similarly, Hoehne et al. (2015) found that individuals at familial risk for depression performed worse on the Iowa Gambling Task compared with controls. In contrast with these findings, Bauer et al. (2016) found no difference between healthy siblings of individuals with bipolar disorder compared with controls on the Cambridge Gambling Task. However, psychotic features within bipolar disorder were not assessed, therefore it is not known whether this impacted sample findings. Additional research in decision-making behaviour in individuals at familial risk for psychotic and non-psychotic SMI is recommended in order to further clarify this field of research.

3.5.2. Verbal memory and familial risk for psychotic severe mental illness

One of the largest effect size differences was observed in poorer verbal memory performance among psychotic SMI offspring compared with controls. Specifically, offspring at familial high risk for psychotic SMI showed moderate impairment in verbal

working memory and verbal memory and learning. These findings are consistent with a previous study, which found that offspring of parents with schizophrenia showed impairments in verbal working memory and verbal learning and memory (de la Serna et al., 2017). Our results extend those findings to suggest that specific impairments in verbal learning and memory are present in offspring at risk of transdiagnostic psychotic SMI regardless of diagnostic classification.

3.5.3. Verbal working memory, sustained attention, and familial risk for psychotic severe mental illness

In the present study, we found the most substantial differences in cognition between offspring of parents with psychotic SMI and controls in the domains of sustained attention and verbal working memory. This is in line with previous findings of impairment in sustained attention and working memory performance among individuals at familial risk for schizophrenia (Giakoumaki, Roussos, Pallis, & Bitsios, 2011; Hemager et al., 2018). Our findings indicate that these deficits are present early in development, and can be detected among offspring at familial risk of SMI before the onset of major mood or psychotic disorders. These results indicate that sustained attention and working memory deficits may not be specific to familial risk for any single disorder; rather they may be associated with transdiagnostic familial risk for psychotic SMI.

3.5.4 Implications for intervention and prevention

These findings have implications for targeted early interventions for offspring of parents with SMI. Early interventions could aim to target cognitive development to minimize the risk of SMI onset among individuals at familial risk. This is supported by previous findings that early intervention targeting cognitive performance in offspring of mothers with major depressive disorder benefits both child cognition and maternal mental health (Maselko et al., 2015). Early interventions may also target parenting skills and the parent-child relationship. Such interventions have previously been shown to have protective effects on children's cognitive development (Cicchetti, Rogosch, & Toth, 2000). In addition, targeted Cognitive Enhancement Therapy has shown large improvements in social cognition for individuals in early and first-episode psychosis (Eack et al., 2011; Eack, Hogarty, Greenwald, Hogarty, & Keshavan, 2007). However, there are currently no data on the effects of early interventions aimed at cognitive remediation on long-term prevalence rates of SMI and the social and functional impact of these disorders among those at familial risk. Longitudinal intervention research is needed to investigate the long-term impact of early interventions targeting cognitive development in offspring of parents affected with SMI.

3.5.5 Limitations

These results should be interpreted in the context of several limitations. First, the present sample included relatively few offspring of parents with schizophrenia. Thus, we were unable to perform meaningful analyses of parents with broadly defined psychotic illness versus parents with schizophrenia diagnosis, specifically. Second, several of the tests were only standardized and validated for a subset of the full age range. In addition,

some tests were added to the assessment battery at follow-up due to the longitudinal nature of the *Families Overcoming Risks and Building Opportunities for Well-being* study. Therefore, some analyses may have been underpowered to detect effects. However, no systematic pattern of missing data was found upon further analysis.

3.5.6. Strengths

The present sample includes a large, well-characterized cohort of children at familial risk for SMI. All offspring assessors were blind to information on parent psychopathology. The comprehensive assessment battery consisted of validated paper-and-pencil cognitive tasks as well as novel computer-based executive function and attention tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB). Offspring of affected parents were systematically recruited via their parents contact with mental health services. Additionally, we ensured that control offspring were approximately matched with offspring of affected parents on socioeconomic factors by selectively recruiting control offspring from the same schools and neighborhoods of the offspring of affected parents. We provided ongoing training meetings for all clinical and cognitive assessors, and all cognitive data was double scored by a core group of research staff to ensure high fidelity data. Finally, due to the well-characterized nature of our cohort, we were able to account for socioeconomic status and common offspring diagnoses in sensitivity analyses.

3.5.7. Conclusion

Widespread mild-to-moderate cognitive impairments are present in young offspring at familial risk for transdiagnostic psychotic SMI. Offspring at familial risk for non-psychotic SMI showed fewer impairments in verbal intelligence, visual memory and decision-making. Future research may examine the development of early interventions targeting cognition and the longitudinal impact for individuals at familial high-risk for SMI.

CHAPTER 4

Study 2: COGNITIVE PERFORMANCE IN YOUTH WITH AND WITHOUT PSYCHOTIC SYMPTOMS

Copyright Statement

This chapter is based on a manuscript that will be submitted as: Lynn E. MacKenzie, Sheri Rempel, Emily Howes Vallis, Alyson Zwicker, Vlad Drobinin, Holly van Gestel, Barbara Pavlova, Rudolf Uher. Cognitive performance in youth with and without psychotic symptoms.

Contribution Statement

I drafted the manuscript, completed the data analysis, and devised the original idea for the chapter. I received guidance and editing from Dr. Rudolf Uher, Dr. Sherry Stewart, Dr. Kim Good, and the other co-authors. Data were collected by the FORBOW research team. I collected data and assisted with the ongoing training of the cognitive and clinical assessors.

4.1 Abstract

Background: Schizophrenia and psychotic disorders are complex conditions with a strong neurodevelopmental basis. Isolated psychotic symptoms are common in childhood and adolescence and indicate vulnerability to psychotic disorders. Prevalence of psychotic symptoms in childhood and adolescence is higher among individuals at familial risk for mental illness. Impaired cognition may be an important marker of neurodevelopmental disturbance and propensity to experience psychotic symptoms.

Methods: In a cohort of 295 youth (mean age 12.07, range 7-24 years) enriched for familial risk of severe mental illness, we assessed psychotic symptoms using validated semi-structured interviews. We assessed a wide range of cognitive functions with a comprehensive battery of paper-and-pencil cognitive tests and computerized tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB).

Results: Of the 295 youth, 71 (24%) reported definite psychotic symptoms. Psychotic symptoms were associated with worse performance in overall cognition (OR = 2.43, 95%CI 1.12 to 5.27, $p = 0.024$). This association remained significant after controlling for age, sex, familial clustering, socioeconomic status, cannabis use, hot executive function, and offspring lifetime diagnoses of ADHD and Anxiety Disorders. Impairment in 6 of the 15 cognitive tests was nominally associated with psychotic symptoms, including vocabulary (OR = 1.43, 95%CI 1.02 to 2.01, p = 0.041), similarities (OR = 1.45, 95% CI 1.03 to 2.05, p = 0.034), visual memory (OR = 1.61, 95% CI 1.06 to 2.46, p = 0.026), hot decision-making (OR = 1.96, 95% CI 1.18 to 3.24, p = 0.009), spatial

working memory (OR = 1.67, 95% CI 1.09 to 2.53, p = 0.019), and set shifting (OR = 1.87, 95% CI 1.21 to 2.88, p = 0.005). No individual cognitive domain was statistically significant after Bonferroni correction.

Conclusions: Broad impairment in cognitive performance may be an early indicator of risk for severe mental illness.

Keywords: *Psychotic symptoms, subclinical psychotic experiences, psychotic-like experiences, cognitive function, cognitive impairment, neurodevelopment, developmental psychopathology*

4.2 Introduction

Current models of psychosis have proposed a neurodevelopmental continuum of symptoms from isolated, subclinical psychotic symptoms with little to no impairment to psychotic disorders with severe functional impairment (Rapoport, Addington, Frangou, & Psych, 2005; Rapoport, Giedd, & Gogtay, 2012). Subclinical psychotic symptoms include hallucinations and delusions, which are indistinguishable from symptoms occurring in psychotic disorders (Kelleher et al., 2012a, 2012b). Psychotic symptoms are common in youth and occur in 10-17% of children and 8% of adolescents in the general population. Higher rates have been reported among youth at familial risk for severe mental illness, including schizophrenia and psychotic disorders, bipolar disorder, and major depressive disorder (Fonville et al., 2015; Polanczyk et al., 2010; Zammit, Hamshere, et al., 2013; Zammit, Kounali, et al., 2013). Psychotic symptoms in childhood and adolescence strongly predict the onset of major mood and psychotic disorders in adulthood (Van Os, Jones, Lewis, Wadsworth, 1997; Sigurdsson, Fombonne, Sayal, Checkley, 1999). Therefore, psychotic symptoms may be an early manifestation of liability for a range of mental disorders and understanding their development may inform early identification of individuals at risk.

Cognitive impairment is a feature of schizophrenia and psychotic disorders (Bora, 2015), and a strong predictor of long-term prognosis and functional impairment (Green, 1996). Milder forms of cognitive impairment are also present among unaffected relatives of individuals with schizophrenia, bipolar disorder and major depressive disorder (Bora et al., 2009; Calafiore et al., 2018; MacKenzie et al., 2019; Snitz et al., 2006), suggesting that cognitive impairment is a marker of familial risk and not solely a

consequence of severe mental illness and psychotropic medication. Individuals with psychotic symptoms who do not meet full criteria for a psychotic disorder perform worse on cognitive tests, including tests of processing speed, attention, and executive functions such as working memory (Fonville et al., 2015; Kelleher et al., 2013; Ziermans, 2013). Impairment in specific domains of cognitive function, including hot versus cold executive function (MacKenzie et al., 2017), processing speed and attention (Niarchou et al., 2013) have been associated with propensity to experience psychotic symptoms. This pattern lends support to the neurodevelopmental model of progressive cognitive impairment along the psychosis continuum. However, it is not yet known whether early impairment in overall cognitive function is associated with psychotic symptoms.

Although overall cognition may be an important early neurodevelopmental indicator of propensity to severe mental illness, previous investigations have not examined the association between psychotic symptoms during childhood and adolescence and cognition using a full cognitive battery. In the present study we aimed to investigate a broad range of cognitive functions using standardized paper-and-pencil cognitive tests and computerized executive function and sustained attention tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB) to test whether previously unexplored cognitive domains are associated with psychotic symptoms. We hypothesized that mild impairment in overall cognitive function would be associated with psychotic symptoms. We also investigated the impact of previously unexplored and potentially confounding variables, including cannabis use, socioeconomic status, and lifetime diagnoses of ADHD and anxiety disorders.

4.3 Methods

4.3.1. Sample description

We investigated the relationship between cognitive performance and psychotic symptoms in 295 participants (age range 7 to 24 years) as part of the *Families Overcoming Risks and Building Opportunities for Well-being* (FORBOW) study, a longitudinal cohort enriched for offspring of parents with severe mental illness (Uher et al., 2014). We assessed participants with cognitive tasks and clinical interviews at 12-month intervals, with a mean of 2.73 assessments completed per participant (range 1-6). Sons and daughters of parents with severe mental illness (SMI) were recruited through mental health clinicians in Nova Scotia, Canada, who systematically inquired whether patients with psychotic and major mood disorders had children in the eligible age range. Offspring participants were included regardless of whether they had current psychopathology or not. Partnership with the Nova Scotia Department of Community Services enabled enrollment of all biological parent and offspring, including sons and daughters not in the care of their biological parents. Control parents were recruited through local school boards and other community organizations (*e.g.,* daycares). In the present study, we included participants who met the following criteria: (1) aged at least 7 years (due to validity of psychotic symptom assessment from age 7 and up) (2) English is the primary language spoken in the home (no translation available for neuropsychological measures). We excluded participants with Full Scale Intelligence Quotient scores less than 70, or intellectual disability to a degree that would invalidate verbal assessment. Ethical approval of the study was granted through the Research Ethics Board of the Nova Scotia Health Authority. All participants with capacity provided written informed

consent. For children who did not have capacity to make an informed choice, a substitute decision maker (biological parent or legal guardian) provided written informed consent and the child provided written assent.

4.3.2 Cognitive assessment

The cognitive battery was designed to assess a range of functions using standardized, paper-and-pencil cognitive tests and computerized tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB) (Sahakian, 1992). We assessed general intelligence with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Verbal learning was assessed with the California Verbal Learning Test, Children's Version (CVLT-C) (Delis, 2000) (among participants aged 7-15 years) and California Verbal Learning Test, Second Edition (CVLT-II) (Delis et al., 1994) (among participants aged 16-24 years). We assessed verbal story memory with the Children's Memory Scale (CMS) (Cohen, 1997) (among participants aged 7-15 years) and Wechsler Memory Scale (WMS) (Wechsler, 1997) (among participants aged 16-24 years). Visual memory was assessed using the Benton Visual Retention Test (Benton, 1974) (among participants aged 8-24 years). We assessed processing speed with the Digit Symbol Coding subtest of the WISC-IV (among participants aged 7-15 years) and the WAIS-IV (Wechsler, 2003, 2008) (among participants aged 16-24 years). We measured cold executive functions using the following tests: (1) verbal working memory using Letter Number Sequencing subtest of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (among participants aged 7-15 years) and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (among participants aged 16-24 years) (2) verbal fluency with the Letter Fluency subtest of the Delis Kaplan Executive Functioning

System (Delis et al., 2001a) (among participants aged 8-24 years) (3) visual working memory using the Spatial Working Memory subtest from the CANTAB battery (among participants aged 7-24 years), (4) cognitive inhibition using the Stop Signal Task subtest from the CANTAB battery (among participants aged 7-24 years) (5) set shifting using the Intra/Extra Dimensional Set Shifting subtest from the CANTAB battery (among participants aged 7-24 years). We measured hot or emotion-laded executive function using the Cambridge Gambling Task (among participants aged 8-24 years). Finally, we measured sustained attention using the rapid visual processing task from the CANTAB battery (among participants aged 7-24 years). One primary variable from each task was selected *a priori* as the best estimate of the function of the task. In the present study, only the participant's first completion of each cognitive measure was analyzed. There were no repeated assessments of cognitive data included in this analysis. Full details of the cognitive battery are listed in Chapter 2.

4.3.3 Assessment of psychotic symptoms

Psychotic symptoms were assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS), Funny Feelings instrument (FF), Schizophrenia Proneness Instrument Child and Youth Version (SPI-CY), and Structured Interview for Prodromal Syndromes (SIPS). In order to maximize statistical power, the present study includes repeated assessments of psychotic symptoms.

Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL) and Structured Clinical Interview for DSM-5. Interviewers blind to parent psychopathology assessed all youth using the K-SADS-PL (Kaufman, 1997). Psychotic symptoms were determined based on DSM-IV criteria using the K-SADS-PL

for youth aged 7 to 17 years and with the Structured Clinical Interview for DSM-5 (SCID-5) (First, 2015) for young adults aged 18 years and older. Presence of psychotic symptoms was confirmed in consensus meetings with psychologists and psychiatrists blind to information on parent psychopathology. We used the K-SADS-PL and SCID-5 psychosis modules and appendix to assess psychotic symptoms, which were also consensus rated by psychologists and psychiatrists blind to parent psychopathology. In analyses, we only considered psychotic symptoms rated as 'definite' by two independent raters.

Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003). In participants aged 12 years and older, we also assessed psychotic symptoms with the SIPS. This interview allows for the identification of attenuated psychotic symptoms and 'at risk mental state' for psychosis (Miller, 2003). In analyses we only considered SIPS ratings scored 3 and above that meet clinical threshold for at risk mental state.

Funny Feelings (Arsenault, 2011). We assessed self-reported psychotic symptoms with the 'Funny Feelings' interview, where the self-reported answers to seven questions was further explored with probes and independent clinical curation (Arsenault, 2011). We recorded frequency, distress, impairment and appraisal for each symptom. We submitted the verbatim transcript of each reported experience for independent clinical curation (blind to parent psychopathology) to establish a psychotic character of the experience, rated as none, probable or definite. In analyses, we only considered psychotic symptoms curated as 'definite' by consensus between two independent raters.

Schizophrenia Proneness Instrument Child and Youth Version (SPI-CY) (Fux et al., 2013). We interviewed participants aged 8 to 24 years with the SPI-CY to assess

basic symptoms. Basic symptoms are subjectively perceived deficits and abnormalities in multiple domains (perception, cognition, language, feelings) and often represent early manifestations of psychosis. Basic symptoms have been shown to strongly and specifically predict the development of schizophrenia (Klosterkotter, 2001). In analyses, we only considered basic symptoms fulfilling criteria for the high-risk profiles of cognitive disturbances (COGDIS) or cognitive-perceptive basic symptoms (COPER) that were shown to predict psychosis with high specificity (Schultze-Lutter, 2012).

4.3.4 Socioeconomic status

Socioeconomic status (SES) was assessed in interviews with parents and indexed by an ordinal variable constructed as a composite of five binary variables: maternal and paternal education beyond high school, whether the family owns their primary residence, household annual income above $60,000, and family home having at least as many bedrooms as residents. The composite score ranged from 0 to 5, with a higher value indicating higher SES. Socioeconomic status was used in sensitivity analyses to further probe the association between overall cognitive performance and propensity to experience psychotic symptoms.

4.3.5. Cannabis use

We assessed cannabis use with semi-structured clinical interviews and validated substance use questionnaires. A composite variable was constructed, including any cannabis use reported on the Drug Use Screening Inventory (DUSI), and/or any cannabis use or cannabis use disorder collected via the K-SADS or SCID clinical interview. Participants completed the DUSI questionnaire every 12 months, and were asked to indicate how many times each month they have used cannabis in the past month. Ratings

included 0 times, 1-2 times, 3-9 times, 10-20 times, more than 20 times. In analyses, we considered any ranking above 1 or more times on the DUSI or any reported cannabis use or diagnosis of cannabis use disorder on the K-SADS or SCID clinical interview (0 = never used cannabis, 1 = used cannabis 1 or more times or meets criteria for cannabis abuse or dependence). The binary cannabis use variable was used in sensitivity analyses to test the primary analysis.

4.3.6 Assessment of psychopathology

Trained interviewers blind to parent diagnoses assessed offspring psychopathology by conducting semi-structured interviews with youth aged 7 to 17 years using the K-SADS-PL (Kaufman et al., 1997), and young adults aged 18 years and older using the SCID-5 (First, 2015). Diagnoses for all Axis I disorders were established (based on DSM-IV criteria for the K-SADS-PL and DSM-5 criteria for the SCID-5) in consensus meetings with a psychologist or psychiatrist blind to information on parent psychopathology. Offspring diagnoses of common mental disorders (attention-deficit/hyperactivity disorder (ADHD), anxiety disorders) were used in sensitivity analysis to probe the specificity in the association between performance on overall cognition and psychotic symptoms.

4.3.7. Parent Assessment

DSM-IV and DSM-5 diagnoses were established using the *Schedule for Affective Disorders and Schizophrenia* (SADS-IV (Endicott, 1978)) and the *Structured Clinical Interview for DSM 5 Disorders* (SCID-5 (First, 2015)). If a parent had more than one SMI diagnosis, primary mental disorder was based on an established hierarchy of schizophrenia > bipolar disorder > major depressive disorder (Rasic et al., 2014).

4.3.8. Data Analysis

The primary dependent variable was the presence of psychotic symptoms (1 = definite psychotic symptom, 0 = no psychotic symptom). The primary independent variables were continuous measures of performance on cognitive tasks, standardized to participant's age and sex. Cognitive variables were z-score standardized and coded so that higher scores indicate worse performance. To account for non-independence of observations from siblings, we tested the relationship between cognitive performance and psychotic symptoms using a robust standard error procedure with a sandwich estimator. We first performed a single test of overall cognition composite, constructed as a summary variable averaging measurement across all 15 measures of cognitive ability. The overall cognition score and FSIQ score were strongly correlated ($r = 0.79$) **(Table 4.2)**, therefore FSIQ was omitted from further analyses. Finally, we proceeded to complete domain-specific analyses testing each of the 15 cognitive measures. For domain-specific analyses we report both nominal significance ($p < 0.05$) and significance corrected for the number of cognitive domains tested (15 domains, Bonferroni corrected p threshold value = 0.003). Additional sensitivity analysed tested the effects of socioeconomic status, cannabis use, offspring lifetime diagnoses of anxiety disorders and ADHD on the association between overall cognitive ability and propensity to experience psychotic symptoms. To examine whether the overall result was driven by a previously reported difference (on a smaller sample) in hot (or emotion-laden) executive function between individuals with and without psychotic symptoms, we also tested an alternative overall cognition composite that does not include the hot executive function cognitive test (MacKenzie et al., 2017). Effect sizes were reported as odds ratios and their 95%

confidence intervals (95% CI). Associations with a p-value smaller than 0.05 were considered nominally significant. Associations with p-value less than 0.003 were considered statistically significant after controlling for multiple comparisons. We completed pairwise correlations between all cognitive tests (**Table 4.2**).

4.4 Results

4.4.1 Sample description

Of the 295 participants aged 7 to 24 years, 71 (26.41%) met criteria for at least one definite psychotic symptom. **Table 4.1** presents the demographic and descriptive characteristics of the sample.

4.4.2 Relationship between measures of cognitive ability

The cognitive domains were moderately to strongly correlated with one another (r = 0.31 to 0.61). The overall cognition score and FSIQ score were strongly correlated (r = 0.79), therefore the FSIQ score was omitted from further analyses. No additional correlation reached the recommended cut-off for omitting strongly correlated variables (Vatcheva et al., 2016), therefore all 15 measures were included in further analyses. Table 4.2 presents bivariate correlations between all cognitive tests.

4.4.3 Association between overall cognitive performance and psychotic symptoms

Worse overall cognitive performance was associated with increased risk of psychotic symptoms (OR = 2.43, 95% CI 1.12 to 5.27, p = 0.024) (**Table 4.3; Fig. 4.1**). The association between overall cognitive performance and psychotic symptoms remained significant in sensitivity analyses controlling for hot decision-making (OR = 2.32, 95% CI 1.17 to 4.62, p = 0.016), socioeconomic status (OR = 2.45, 95% CI 1.18 to 5.10, p = 0.017), cannabis use (OR = 2.49, 95% CI 1.20 to 5.16, p = 0.014), and lifetime diagnosis of ADHD (OR = 2.64, 95% CI 1.28 to 5.45, p = 0.009) and anxiety disorders (OR = 2.45, 95% CI 1.22 to 4.91, p = 0.012) (**Table 4.4**).

4.4.4. Association between individual cognitive domains and psychotic symptoms

Worse performance on 6 of the 15 cognitive tests was nominally associated with increased risk of psychotic symptoms, including vocabulary (OR = 1.43, 95% CI 1.02 to 2.01, $p = 0.041$), similarities (OR = 1.45, 95%CI 1.03 to 2.05, $p = 0.034$), Benton Visual Retention Test (OR = 1.61, 95%CI 1.06 to 2.46, $p = 0.026$), Cambridge gambling task (OR = 1.96, 95%CI 1.18 to 3.24, $p = 0.009$), spatial working memory (OR = 1.67, 95%CI 1.09 to 2.53, $p = 0.019$), and the intra/extra dimensional set shifting task (OR = 1.87, 95% 1.21 to 2.88, $p = 0.005$) (**Table 4.3; Fig. 4.1**). No individual cognitive domain was statistically significant after correction for multiple comparisons.

We found no association between performance intelligence subtests of the Wechsler Abbreviated Scale of Intelligence, verbal working memory, verbal learning, digit symbol coding, story memory, verbal fluency, stop signal task and risk of psychotic symptoms.

4.4.5. Association between familial risk for psychotic and non-psychotic severe mental illness and prevalence of psychotic symptoms in offspring

Parent diagnosis of any SMI was associated with increased risk to experience psychotic symptoms in offspring (OR = 2.59, 95% CI 1.07 to 6.29, $p = 0.036$). In contrast to the secondary hypothesis for study 2, we found no specific association between parent diagnosis of psychotic SMI and offspring psychotic symptoms (OR = 1.40, 95% CI 0.63 to 3.08, $p = 0.405$).

Table 4.1. Demographic variables and clinical characteristics of youth with and without psychotic symptoms

	PSY (n=71)		No-PSY (n= 224)			
	Mean	SD	Mean	SD	t-statistic	p-value
Age	13.87	3.90	12.34	3.46	-3.15	0.002
SES	2.63	1.31	3.14	1.42	2.68	0.009
	Count	(%)	Count	(%)	Chi^2	p-value
Male	34	47.89%	110	49.11%	0.03	0.858
Female	37	52.11%	114	50.89%		
Parent primary diagnosis						
MDD	30	42.25%	98	43.75%	14.47	0.002
BD	27	38.03%	41	18.30%		
SCH	2	2.82%	12	5.36%		
Control	12	16.90%	73	32.59%		
Parent psychotic symptoms	20	28.17%	47	20.98%	1.59	0.208
Offspring diagnoses						
ADHD	9	12.68%	28	12.50%	0.00	0.969
Anxiety Disorder	27	38.03%	45	20.09%	9.40	0.002
MDD	2	2.82%	11	4.91%	0.56	0.454

Note. **N=295.** PSY = Psychotic symptom group, No-PSY = No psychotic symptom group, SD = Standard Deviation, SES = Socioeconomic Status, MDD = Major Depressive Disorder, BD = Bipolar Disorder, SCH = Schizophrenia and psychotic disorders, ADHD = Attention-Deficit/Hyperactivity Disorder.

Table 4.2. Correlations between cognitive tasks

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Overall Cognition	1																
2. FSIQ	0.79	1															
3. Block Design	0.54	0.58	1														
4. Matrix Reasoning	0.61	0.61	0.45	1													
5. Vocabulary	0.75	0.69	0.33	0.40	1												
6. Similarities	0.65	0.64	0.31	0.39	0.61	1											
7. LNS	0.63	0.44	0.28	0.39	0.33	0.30	1										
8. Coding	0.57	0.33	0.21	0.16	0.23	0.26	0.39	1									
9. CVLT	0.57	0.37	0.16	0.24	0.28	0.30	0.33	0.38	1								
10. Story Memory	0.51	0.31	0.05	0.11	0.31	0.32	0.22	0.19	0.35	1							
11. Verbal Fluency	0.49	0.32	0.12	0.15	0.25	0.28	0.19	0.33	0.38	0.21	1						
12. BVRT	0.55	0.45	0.36	0.31	0.28	0.26	0.27	0.18	0.16	0.13	0.14	1					
13. CGT	0.47	0.26	0.14	0.15	0.16	0.16	0.14	0.19	0.08	0.11	0.07	0.30	1				
14. SWM	0.53	0.32	0.20	0.21	0.10	0.13	0.22	0.20	0.22	0.19	0.16	0.36	0.40	1			
15. IED	0.49	0.26	0.24	0.14	0.13	0.16	0.18	0.09	0.07	0.17	0.09	0.28	0.20	0.29	1		
16.SST	0.19	0.06	0.08	0.09	-0.01	0.00	0.07	-0.04	0.09	-0.01	0.15	0.17	0.07	0.19	0.15	1	
17. RVP	0.49	0.25	0.12	0.19	0.17	0.17	0.23	0.25	0.18	0.18	0.14	-0.00	0.14	0.02	0.16	-0.09	1

Note. **N=295.** FSIQ = Full Scale Intelligence Quotient, LNS = Letter Number Sequencing, Coding = Digit Symbol Coding, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, CGT = Cambridge Gambling Task, SWM=Spatial Working Memory, IED = Intra/Extra Dimensional Set Shifting, SST = Stop Signal Task, RVP = Rapid Visual Processing Task.

Table 4.3. Performance on cognitive tasks among youth with and without psychotic symptoms

	PSY		No-PSY		Effects of performance on the risks of experiencing psychotic symptoms					
Cognitive Test	Mean	S.D.	Mean	S.D.	Odds Ratio	SE	z	p-value	95% CI Lower	95% CI Upper
Overall cognition	-0.12	0.57	0.06	0.59	2.43	0.96	2.25	0.024	1.12	5.27
Vocabulary	101.55	14.71	104.59	16.07	1.43	0.25	2.05	0.041	1.02	2.01
Similarities	97.66	14.15	100.80	15.57	1.45	0.26	2.12	0.034	1.03	2.05
Block Design	105.66	13.24	101.15	16.04	1.17	0.21	0.84	0.400	0.81	1.67
Matrix Reasoning	106.24	14.59	103.37	15.86	0.97	0.17	-0.17	0.861	0.68	1.38
LNS	99.73	13.99	101.95	15.14	1.14	0.19	0.78	0.436	0.82	1.58
CVLT	103.62	14.45	105.72	16.00	1.08	0.17	0.46	0.643	0.78	1.48
BVRT	6.89	1.98	7.47	1.59	1.61	0.35	2.23	0.026	1.06	2.46
Coding	88.73	12.56	92.76	13.16	1.28	0.24	1.35	0.177	0.89	1.84
Story Memory	103.96	20.05	104.29	19.88	0.93	0.17	-0.39	0.698	0.65	1.33
Verbal Fluency	99.59	24.67	104.52	20.79	1.31	0.27	1.36	0.172	0.89	1.95
CGT	-0.16	0.80	0.07	0.75	1.96	0.50	2.61	0.009	1.18	3.24
SWM	0.12	0.92	-0.10	0.99	1.67	0.36	2.34	0.019	1.09	2.53
IED	0.14	1.07	-0.21	0.93	1.87	0.42	2.82	0.005	1.21	2.88
SST	0.38	0.58	0.45	0.50	1.20	0.26	0.81	0.417	0.78	1.84
RVP	-0.17	1.13	0.16	0.92	1.43	0.28	0.29	0.075	0.96	2.11

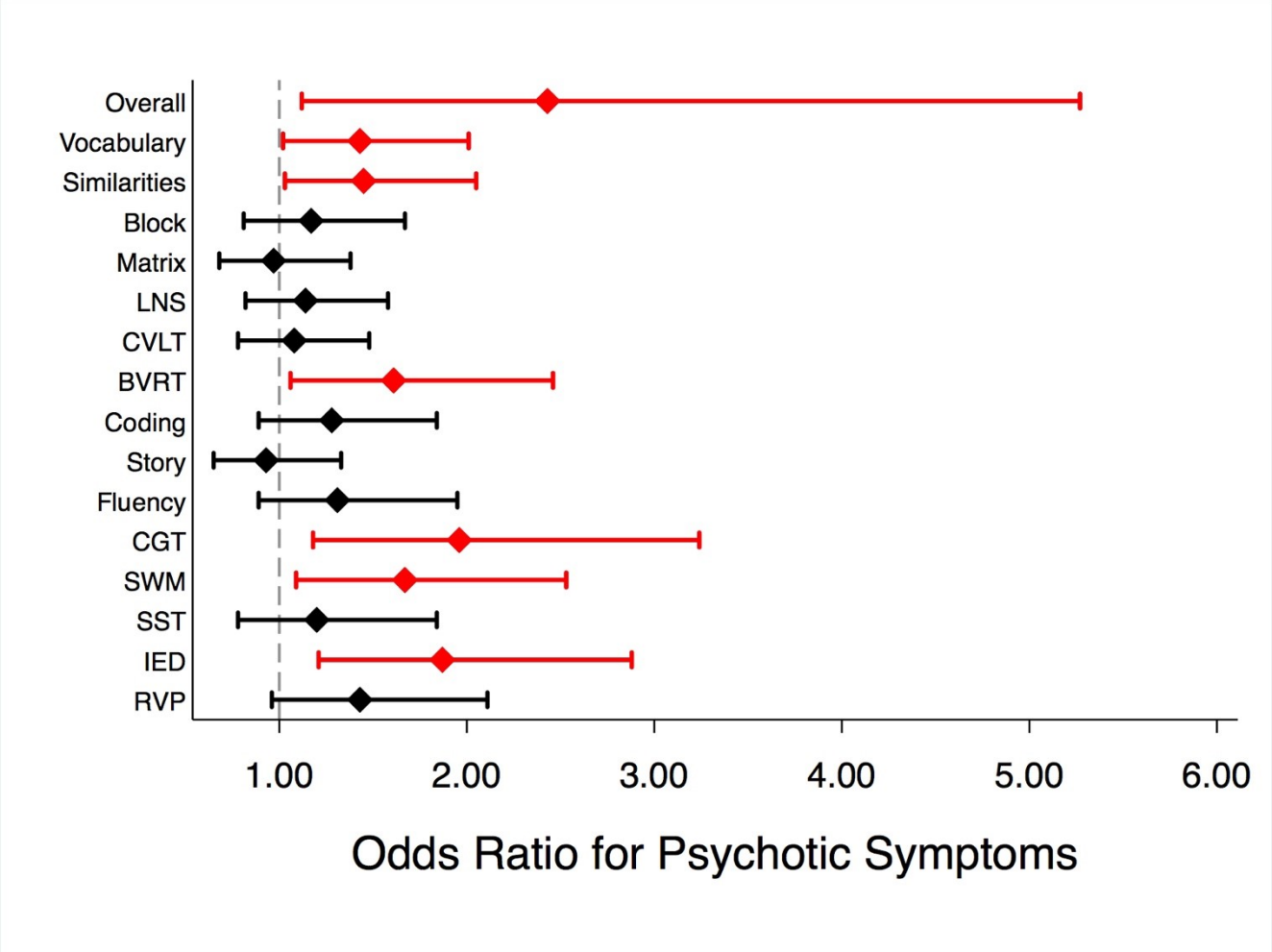
Note. **N=295.** SE = Standard Error, 95% CI = 95 percent confidence interval, LNS = Letter Number Sequencing, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, Coding = Digit Symbol Coding, CGT = Cambridge Gambling Task, SWM=Spatial working memory, IED = Intra/Extra Dimensional Set Shifting, SST = Signal Stop Task, RVP = Rapid Visual Processing Task.

Table 4.4 Sensitivity analyses probing the effect of sample characteristics on overall cognitive performance and psychotic symptoms

Sensitivity Analysis	Odds Ratio	SE	p-value	95% CI Lower	95% CI Upper
Cannabis use	2.49	0.93	0.014	1.20	5.16
Socioeconomic Status	2.45	0.92	0.017	1.18	5.10
Omitted Hot EF	2.32	0.82	0.016	1.17	4.62
ADHD	2.64	0.98	0.009	1.28	5.45
Anxiety Disorders	2.45	0.87	0.012	1.22	4.91

Note. **N = 295.** SE = Standard Error, 95% CI = 95% confidence interval, EF = Executive Function, ADHD = Attention Deficit Hyperactivity Disorder

Figure 4.1. Performance on cognitive tests and propensity for psychotic symptoms



Note. **N=295.** Overall = Overall cognitive performance, Block = Block Design, Matrix = Matrix Reasoning, LNS = Letter Number Sequencing, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, Coding = Digit Symbol Coding, Story = Story Memory, Fluency = verbal fluency, CGT = Cambridge Gambling Task, SWM = Spatial working memory, SST = stop signal task, IED = Intra/Extra Dimensional Set Shifting, RVP = Rapid Visual Processing task. Results shown in red are nominally significant (p<.05). Error bars represent the lower and upper bound of the 95% CI for the Odds Ratio.

4.5 Discussion

In the present study, we found a robust association between overall cognitive ability and psychotic symptoms, where individuals experiencing psychotic symptoms showed lower cognitive performance on average than individuals who did not experience psychotic symptoms. This finding remained after controlling for socioeconomic status, cannabis use, hot executive function, and offspring lifetime diagnoses of ADHD and anxiety disorders. Impairment in 6 of the 15 specific cognitive tests was nominally associated with psychotic symptoms, including vocabulary, similarities, visual memory, hot decision-making, spatial working memory, and set shifting. However, no individual cognitive domain was statistically significant after correction for multiple comparisons. We found no significant association between psychotic symptoms and performance IQ, letter number sequencing, verbal learning, processing speed, verbal fluency, cognitive inhibition, or sustained attention.

These findings have implications for the neurodevelopmental model of the psychosis continuum. Progressive degrees of cognitive impairment have been observed along the spectrum of psychotic illness, from slightly lower cognitive ability among healthy first-degree relatives of affected individuals (Bora et al., 2009; MacKenzie et al., 2019; Snitz et al., 2006) and among individuals experiencing isolated psychotic symptoms (Cullen et al., 2010; Dickson et al., 2014), to moderately lowered cognitive ability among individuals at clinical-high risk for psychosis (Hou et al., 2016) and substantially lowered cognitive ability among individuals with diagnosed psychotic disorder (Aleman, Hijman, de Haan, & Kahn, 1999; Schaefer, Giangrande, Weinberger, & Dickinson, 2013). It has been reported that specific impairments in processing speed

at age 8 years and attention at age 11 years were associated with psychotic symptoms at age 12 years in a general population sample (Niarchou et al., 2013). It should be noted that the effects observed in this general population sample were weaker than those observed in the present study, which may be due to the enrichment for familial risk of SMI in our sample. Our results extend upon previous findings to indicate that impairment in overall cognitive performance is associated with psychotic symptoms.

In the present study, we found nominal differences in cognitive performance between youth with and without psychotic symptoms within three tests of executive function, including decision-making, set shifting, and spatial working memory. Deficits in these higher-order cognitive functions are common throughout the psychosis continuum (Blanchard et al., 2010; Cullen et al., 2010; Kelleher et al., 2013; Kelleher et al., 2012) and represent a central feature of impairment among individuals diagnosed with a psychotic disorder (Orellana & Slachevsky, 2013). In a previous study on a smaller subset of our cohort, we found that worse hot decision-making performance was associated with increased risk of psychotic symptoms (MacKenzie et al., 2017). In the present study, which includes a broader range of cognitive tests in a larger sample, we found that overall cognitive performance was associated with psychotic symptoms, independent of hot decision-making ability. This indicates that although hot executive function may have a particularly strong relationship with psychotic symptoms, cold executive function is also associated with the propensity to experience psychotic symptoms. This pattern of results may suggest the involvement of frontal lobe neural circuits in the etiopathology of psychotic symptoms.

In the present study, we also found that worse performance on tests of verbal intelligence, but not performance intelligence, was nominally associated with psychotic symptoms. This is consistent with previous findings, which found that lower verbal cognitive ability at age 8 years and greater verbal developmental lag between ages 8-15 years were associated with psychotic symptoms in adulthood (Koike, Barnett, Jones, & Richards, 2018). Koike et al. (2018) also found no association between non-verbal cognition and psychotic symptoms. Childhood performance on tasks assessing verbal cognition has also been associated with psychotic disorders in adulthood (Seidman et al., 2013). Our findings suggest that verbal cognitive ability may be more strongly associated with psychotic symptoms than non-verbal cognitive ability. This highlights the importance of utilizing a wide range of functions when assessing association between cognitive abilities and psychotic symptoms.

The present study benefited from the enrichment for familial risk of severe mental illness within our cohort and the comprehensive assessment of cognitive ability using a broad battery of cognitive tests. Due to the well-characterized nature of our sample, we were also able to investigate the impact of previously unexplored and potentially confounding variables on the relationship between cognition and psychotic symptoms, including cannabis use, socioeconomic status, and lifetime diagnoses of ADHD and anxiety disorders. We also benefited from the assessment of psychotic symptoms using semi-structured interview measures by assessors blinded to parent psychopathology and independent clinical curation.

Despite these strengths, our findings should be interpreted in the context of several limitations. First, it was not possible to determine the direction of cause and

effect. Among the individuals who experienced psychotic symptoms, these symptoms were present both before and after completing the cognitive tasks. Therefore, it was not possible to determine whether impairment in overall cognitive performance was associated with increased propensity to experience psychotic symptoms or whether the presence of psychotic symptoms led to deficits in cognition. Second, although our study was sufficiently powered to detect the moderate effects we found between overall cognitive performance and psychotic symptoms, it may have been underpowered to detect smaller effects in specific domains. This was apparent when comparing our non-significant sustained attention effect size (OR = 1.43, 95% CI 0.96 to 2.11) with previous reports of a significantly increased risk for psychotic symptoms in youth with worse performance on attention tasks (OR = 1.14, 95% CI 1.04 to 1.25) (Niarchou et al., 2013).

4.6 Conclusion

In conclusion, the present study found an association between worse performance on overall cognition and propensity to experience psychotic symptoms during childhood and adolescence. These findings suggest that deficits in cognitive function may reflect liability for the development of SMI. Evidence indicates that it is possible to improve cognitive functioning through early intervention (Diamond & Lee, 2011; Singla, Kumbakumba, & Aboud, 2015). Therefore, young people who experience psychotic symptoms represent an important population in need of early interventions targeting cognitive functioning, which may reduce the long-term risk of severe mental illness.

CHAPTER 5

Study 3: COGNITIVE PERFORMANCE PREDICTS ONSET OF SEVERE MENTAL ILLNESS IN INDIVIDUALS AT FAMILIAL RISK

Copyright Statement

This chapter is based on a manuscript that will be submitted as: Lynn E. MacKenzie, Sheri Rempel, Emily Howes Vallis, Alyson Zwicker, Vlad Drobinin, Holly van Gestel, Barbara Pavlova, Rudolf Uher. Cognitive performance predicts onset of severe mental illness in individuals at familial risk.

Contribution Statement

I drafted the manuscript, completed the data analysis, and devised the original idea for the chapter. I received guidance and editing from Dr. Rudolf Uher, Dr. Sherry Stewart, Dr. Kim Good, and the other co-authors. Data were collected by the FORBOW research team. I collected data and assisted with the ongoing training of the cognitive and clinical assessors.

5.1 Abstract

Background. Cognitive impairment is a feature of severe mental illness (SMI), including schizophrenia, bipolar disorders, and severe major depressive disorder. Mild deficits in cognitive ability have also been reported in first-degree relatives of individuals with SMI. Mild impairment in cognition may index increased liability to SMI and provide clues to etiology and prevention. To uncover the etiological mechanisms behind the development of SMI, it is important to clarify which domains of cognitive functions are most strongly related to the development of SMI.

Methods. In a prospective longitudinal cohort of 309 youth (followed for up to 6 years, mean follow-up time 2.73 years) enriched for familial risk for SMI, we measured cognitive performance with standardized paper-and-pencil cognitive tests and computerized tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB). We assessed the onset of severe mental illness using validated semi-structured clinical interviews.

Results. Onset of SMI was predicted by worse performance on overall cognitive performance (OR = 1.50, p = 0.018, 95% CI 1.07 to 2.10). Worse performance on 3 of the 15 cognitive tests were nominally associated with offspring new onset of SMI, including vocabulary (OR = 1.57, p = 0.017, 95% CI 1.08 to 2.29), story memory (OR = 1.60, 95% CI 1.10 to 2.34, p =0.015) and sustained attention (OR = 1.35, p = 0.007, 95% CI 1.08 to 1.68). The association between worse performance on overall cognition and offspring new onset of SMI diagnosis remained significant in sensitivity analyses

controlling for cannabis use, socioeconomic status, and lifetime diagnosis of Anxiety Disorders and ADHD.

Conclusions. Impairments in overall cognition, verbal cognition, story memory, and sustained attention may be indicators of risk and targets for pre-emptive early interventions in individuals at familial risk.

Key words: Cognitive performance, cognitive impairment, offspring of affected parents, severe mental illness, youth at-risk, familial risk, neurodevelopment

5.2 Introduction

Moderate to severe cognitive impairment is a feature of SMIs, including schizophrenia, bipolar disorders, and severe and chronic major depressive disorder. Milder impairments have also been reported in first degree relatives of individuals with major depressive disorder (MacKenzie et al., 2019), bipolar disorder (Bora & Ozerdem, 2017; Bora & Ozerdem, 2017), and schizophrenia and other psychotic disorders (Agnew-Blais & Seidman, 2013). Several large, population-based birth cohort studies have found that cognitive deficits in childhood and adolescence predicts psychotic disorders in adulthood. In the Dunedin cohort, participants who went on to develop schizophreniform disorder at age 26 exhibited deficits in IQ (approximately 0.4 SDs) on five assessments at ages 3, 5, 7, 9, and 11 (Cannon et al., 2002). In line with these findings, in the National Survey of Health and Development, worse performance on IQ tests at ages 11 and 15 was associated with onset of schizophrenia in adulthood (Jones et al., 1994); however, age 8 IQ was unrelated to onset of schizophrenia in adulthood. In the Avon Longitudinal Study of Parents and Children cohort, participants who developed psychotic disorder in adulthood exhibited gradually increasing deficits in Full Scale IQ and nonverbal IQ subtests between 18 months, 4 years, 8 years, 15 years and 20 years of age (Mollon et al., 2018). Participants who developed depression in adulthood exhibited increasing deficits in nonverbal IQ but not FSIQ.

Other prospective studies have found no association between worse cognitive performance and onset of non-psychotic SMI. In a follow-up analysis of the Dunedin birth cohort study, Schaefer et al. (2017) found that IQ performance at age 12 was not associated with onset of major depressive disorder by age 38. Similarly, the National

Child Development birth cohort found no association between IQ performance at ages 7 and 11 and the development of major mood disorders in adulthood. Zammit et al. (2004) found that worse premorbid composite IQ score was associated with the development of schizophrenia, other psychoses, and severe depression, however there was no relationship between IQ and onset of bipolar disorder in a sample of over 50000 male Swedish conscripts (1969-1970) (Zammit et al., 2004). Differences in findings across studies may be due to inconsistencies in research design (e.g., use of registry data and chart diagnoses).

Only one longitudinal cohort study has investigated cognitive performance as predictor of SMI in those at familial risk. Paccalet et al. (2016) followed 84 offspring of parents affected with bipolar disorder or schizophrenia, 15 of which developed new onset major mood and psychotic disorders upon longitudinal follow-up. The authors found a non-significant trend in the specific contribution of cognitive deficits (identified as a -1.0 standard deviation on a composite variable including the performance on the Digit Symbol Substitution Task, California Verbal Learning Test, and the Rey Complex Figure) to the risk for development of SMI. The analysis was not separated by specific cognitive domains, therefore it is not known whether different tests were individually associated with onset of SMI. The accumulation of several risk factors (including cognitive deficits, prior episode of poor social functioning, psychotic symptoms, drug use, and trauma) was associated with the development of SMI.

The mild to moderate cognitive deficits in individuals at familial risk found in study 1 of this thesis may index increased liability to SMI, and provide clues to etiology and prevention. To uncover the etiological mechanisms behind the development of SMI,

it may be important to clarify which domains of cognitive functions are most strongly related to the development of SMI.

It remains unclear whether cognitive impairment increases long-term prevalence rates of SMI development in those at familial risk. In the present study, we aimed to address this gap in knowledge by assessing a wide range of cognitive functions in a longitudinal cohort of sons and daughters of parents affected with SMI. We tested the hypothesis that worse overall cognitive performance is associated with onset of SMI in a longitudinal sample enriched for familial risk of SMI.

5.3 Methods

5.3.1 Participants

In the present study, 309 participants of the *Families Overcoming Risks and Building Opportunities for Wellbeing* (FORBOW (Uher et al., 2014)) longitudinal cohort study were assessed at 12-month intervals between February 2013 and February 2019 (6 time points; mean number of assessments completed per participant 2.73). Participants were referred by their mental health clinicians who systematically inquired whether parents affected with severe mental illness had sons and daughters in the eligible age range (6 to 24). Offspring were recruited regardless of whether they had psychopathology. Healthy control parents and their children were recruited through local school boards. Exclusion criteria included (1) FSIQ < 70, (2) intellectual disability of a degree that would invalidate verbal assessment, (3) English is not the primary language spoken in the home environment (due to lack of comparable validated cognitive tests in other languages), and (4) any offspring diagnosis of SMI at the baseline assessment (i.e., individuals with prior episodes of major depressive disorder, bipolar disorder, and schizophrenia were excluded from this analysis). The Research Ethics Board of the Nova Scotia Health Authority approved the study protocol. All participants with capacity provided written informed consent. For children who did not have capacity to make an informed decision (e.g., typically due to young age), a substitute decision-maker (parent or legal guardian) provided written informed consent and the child provided written or verbal assent.

5.3.2 Longitudinal follow-up procedure

We assessed prior cognitive performance as a predictor of later onset of offspring SMI diagnosis upon longitudinal follow-up in a sample enriched for familial risk. Participants and their parents completed research asesssments every 12-months (or within 1 month earlier or later). Trained research staff blinded to parent psychopathology assessed offspring. Assessors of parents were also blinded to offspring psychopathology. The cognitive protocols were designed in consultation with psychologists in the field. Particular attention was paid to designing protocols that minimized practice effects (e.g., no repetition of executive function tests, WASI completed every 2 years rather than every year) and were not overly burdensome with respect to assessment length (e.g., maximum length between 2-2.5 hours). There were no verbal tasks administered during the story memory delay. Additional detail regarding the annual research assessments is included in Table 2.1 of Chapter 2**.** For a sample of a cognitive protocol, see Appendix A.

5.3.3 Parent Assessment

DSM-IV and DSM-5 diagnoses were established with the *Schedule for Affective Disorders and Schizophrenia* (SADS-IV (Endicott, 1978)) and the *Structured Clinical Interview for DSM 5 Disorders* (SCID-5 (First, 2015)). If a parent had more than one SMI diagnosis, primary parental mental disorder group was based on an *a priori* established hierarchy of schizophrenia > bipolar disorder > major depressive disorder (Rasic et al., 2014). Demographic information was obtained from the parents, including physical health, family income, marital status, and education level of mother, father and/or relevant legal guardians.

5.3.4 Offspring Assessment

5.3.4.1 Clinical Interview.

We established diagnoses of offspring between ages 6-17 with the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL (Kaufman et al., 1997)). Participants aged 18-24 were assessed with the Structured Clinical Interview for DSM-5 (SCID-5 (First, 2015)). All offspring assessors were blind to parent psychopathology and vice versa for the parent assessors. Offspring diagnoses were presented and confirmed in consensus meetings with psychologists and psychiatrists blind to parent psychopathology.

5.3.4.2 Cognition.

The cognitive battery was designed to assess a range of functions using standardized, paper-and-pencil cognitive tests and computerized tasks from the Cambridge Automated Neuropsychological Test Battery (CANTAB) (Sahakian, 1992). We assessed general intelligence with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). We assessed verbal learning with the California Verbal Learning Test, Children's Version (CVLT-C) (Delis, 2000) (among participants aged 7-15 years) and California Verbal Learning Test, Second Edition (CVLT-II) (Delis et al., 1994) (among participants aged 16-24 years). Verbal story memory was assessed with the Children's Memory Scale (CMS) (Cohen, 1997) (among participants aged 7-15 years) and Wechsler Memory Scale (WMS) (Wechsler, 1997) (among participants aged 16-24 years). We assessed visual memory using the Benton Visual Retention Test (Benton, 1974) (among participants aged 8-24 years). We assessed processing speed with the Digit Symbol Coding subtest of the WISC-IV (among participants aged 7-15 years) and the WAIS-IV (Wechsler, 2003, 2008) (among participants aged 16-24 years). We measured cold executive functions using the following subtests: (1) verbal working memory using

Letter Number Sequencing subtest of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (among participants aged 7-15) and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (among participants aged 16-24) (2) verbal fluency with the Letter Fluency subtest of the Delis Kaplan Executive Functioning System (Delis et al., 2001a) (among participants aged 8-24) (3) visual working memory using the Spatial Working Memory subtest from the CANTAB battery (among participants aged 7-24), (4) cognitive inhibition using the Stop Signal Task subtest from the CANTAB battery (among participnats aged 7-24) (5) set shifting using the Intra/Extra Dimensional Set Shifting subtest from the CANTAB battery (among participants aged 7-24). We measured hot executive function using the Cambridge Gambling Task (among participants aged 8-24). Finally, sustained attention was assessed using the Rapid Visual Processing task from the CANTAB battery (among participants aged 7-24). One primary variable from each task was selected *a priori* as the best estimate of the function of the task. Full details of the cognitive battery are listed in Chapter 2 of this thesis.

5.3.4.3 Socioeconomic status.

Socioeconomic status was assessed in interviews with parents and indexed by an ordinal variable constructed as a composite of five binary variables: (1) maternal and (2) paternal education beyond high school, (3) whether the family owns their primary residence, (4) household annual income above $60,000, and (5) family home having at least as many bedrooms as residents. The composite score ranged from 0 to 5, with a higher value indicating higher SES. Socioeconomic status was utilized in sensitivity analyses to further probe the association between overall cognition and onset of SMI in offspring.

5.3.4.4 Cannabis use.

We assessed cannabis use in semi-structured clinical interviews and validated substance use questionnaires. A composite variable was constructed, including any cannabis use reported on the Drug Use Screening Inventory (DUSI), and/or any cannabis use or cannabis use disorder assessed via the K-SADS or SCID clinical interview. Participants completed the DUSI questionnaire every 12 months, and were asked to indicate how many times each month they have used cannabis in the past month. Ratings included 0 times, 1-2 times, 3-9 times, 10-20 times, more than 20 times. In analyses, we considered any ranking above 1 or more times on the DUSI or any reported cannabis use or diagnosis of cannabis use disorder on the K-SADS or SCID clinical interview (0 = never used cannabis, 1 = used cannabis 1 or more times or meets criteria for cannabis use disorder). Cannabis use was used in sensitivity analyses to test the primary analysis.

5.3.5 Data analysis

We investigated the effect of prior cognitive performance on the development of offspring new SMI diagnosis upon longitudinal follow-up assessments. The primary dependent/outcome variable was new onset of severe mental illness in offspring, defined as at least one of the following: (1) major depressive disorder, (2) bipolar disorder, (3) schizophrenia, schizoaffective disorder or other psychotic disorder. Independent/predictor variables were *a priori* selected cognitive performance variables for each task. Cognitive variables were z-score standardized to a mean of 0 and standard deviation of 1 and coded so that higher scores indicate worse performance. The primary analysis was a single test of an overall cognition composite, constructed as a summary variable averaging valid assessment across 15 measures of cognitive ability. The overall cognition score and FSIQ

score were strongly correlated ($r = 0.79$), therefore the FSIQ score was omitted from further analyses. Secondary analyses included each of the 15 domain-specific cognitive scores. For domain-specific analyses we report both nominal significance ($p < .05$) and significance corrected for the number of cognitive domains tested (15 tests; corrected *p*-value threshold = .003). We analyzed the associations between cognitive performance and offspring SMI diagnosis using lagged mixed-effect logistic regression applied in the generalized linear latent and mixed model (GLLAMM (Rabe-Hesketh, 2015)), which permits inclusion of repeated assessments from the same individual and accounts for non-independence of observations from related individuals (siblings) with nested random effects of individual and family. All analyses controlled for participant's age and sex as fixed-effect covariates. We tested whether the effects of cognition on SMI persisted after controlling for effects of socioeconomic status, offspring cannabis use, and lifetime diagnosis of ADHD and anxiety disorders. Effect sizes are reported as odds ratios (ORs) with 95% confidence intervals (95% CIs).

5.4 Results

5.4.1 Sample description

At baseline, 86 control participants and 223 familial risk participants aged 6 to 24 completed assessment. **Table 5.1** presents the demographic and clinical characteristics of the participants at baseline assessment.

At last assessment, 34 (15.25%) of the 223 familial risk participants and 2 (2.33%) of the control participants developed new onset SMI. **Table 5.1** presents demographic and clinical characteristics of the 309 participants at their last assessment.

5.4.2 Association between cognitive performance and onset of SMI

Worse overall cognitive performance was associated with onset of severe mental illness upon follow-up assessments (OR = 1.50, 95% CI 1.07 to 2.10 , p = 0.018) (**Table 5.2; Fig. 5.1**). The association between overall cognitive performance and onset of SMI remained significant in a model controlling for age, sex, clustering of siblings within families, socioeconomic status, cannabis use, and lifetime diagnosis of ADHD and anxiety disorders (**Table 5.3**).

5.4.3 Association between individual cognitive domains and onset of SMI

Worse performance within the domains of verbal intelligence (Vocabulary; OR = 1.57, 95% CI 1.08 to 2.29, p = 0.017), story memory (Story Memory; OR = 1.60, 95% CI 1.10 to 2.34, p =0.015), and ustained attention (Rapid Visual Processing; OR=1.35, 95%CI 1.08 to 1.68, p=0.007) were nominally associated with onset of severe mental illness (**Table 5.2, Fig. 5.1**). No individual cognitive domain was statistically significant after Bonferroni correction.

Table 5.1. Demographic and clinical characteristics of participants with and without new onset SMI diagnoses at baseline and last assessment

	Baseline assessment				Last assessment			
	SMI (n=34)		No-SMI (n=275)		SMI (n=34)		No-SMI (n = 275)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	14.26	3.92	10.24	3.94	17.97	3.91	12.96	4.14
SES	2.31	1.45	3.06	1.33	2.41	1.35	3.16	1.36
	Count	%	Count	%	Count	%	Count	%
Male	14	41.18%	139	50.55%	14	41.18%	139	50.55%
Female	20	58.82%	136	49.45%	20	58.82%	136	49.45%
Parent diagnosis								
MDD	15	44.12%	110	40.00%	15	44.12%	110	40.00%
BD	17	50.00%	60	21.82%	17	50.00%	60	21.82%
SCH	0	0%	21	7.64%	0	0%	21	7.64%
Control	2	5.88%	84	30.54%	2	5.88%	84	30.54%
Parent psychotic symptoms	17	50.00%	64	23.27%	17	50.00%	64	23.27%
Offspring diagnoses								
oMDD	0	0%	0	0%	26	76.47%	0	0.00%
oBD	0	0%	0	0%	4	11.77%	0	0.00%
oSCH	0	0%	0	0%	2	5.88%	0	0.00%
oSCH-A	0	0%	0	0%	2	5.88%	0	0.00%

Note. **N=309.** FR = Familial Risk, SMI = Severe Mental Illness, No-SMI = No Severe Mental Illness, SD = Standard Deviation, SES = Socioeconomic status, MDD = Major Depressive Disorder, BD = Bipolar Disorder, SCH = Schizophrenia and Other Psychotic Disorders, Parent psychotic = Parent psychotic symptoms, oMDD = Offspring new onset of severe major depressive disorder, oBD = Offspring new onset of bipolar disorder, oSCH = offspring new onset of schizophrenia, oSCH-A = Offspring new onset of schizoaffective disorder.

Table 5.2. Performance on cognitive tasks and effects of performance on the risk of new onset severe mental illness diagnosis

	SMI		No-SMI							
Cognitive Test	Mean	S.D.	Mean	S.D.	OR	SE	z	*p*-value	95% CI Lower	95% CI Upper
Overall	-0.20	0.60	-0.10	0.55	1.50	0.26	2.36	0.018	1.07	2.10
Vocabulary	97.81	12.50	102.58	14.22	1.57	0.30	2.39	0.017	1.08	2.29
Similarities	96.42	11.68	100.01	14.06	1.49	0.30	1.93	0.053	0.99	2.22
Block Design	98.88	10.86	99.16	14.54	1.27	0.28	1.08	0.279	0.83	1.94
Matrix	95.70	19.35	100.83	13.76	1.33	0.24	1.60	0.110	0.94	1.90
LNS	96.21	10.66	99.37	15.28	1.37	0.33	1.31	0.189	0.86	2.19
CVLT	102.21	16.29	105.10	17.70	1.21	0.20	1.15	0.252	0.87	1.67
BVRT	-0.09	0.79	0.08	0.98	1.35	0.36	1.11	0.269	0.79	2.28
Coding	89.88	11.06	91.63	13.06	1.22	0.26	0.91	0.364	0.80	1.86
Story	95.45	12.14	106.51	16.50	1.60	0.31	2.43	0.015	1.10	2.34
Fluency	86.88	23.44	99.06	21.39	1.12	0.31	0.42	0.677	0.65	1.93
CGT	-0.16	1.12	0.19	1.11	0.98	0.18	-0.12	0.902	0.68	1.09
SWM	0.42	0.91	-0.01	1.03	1.05	0.23	0.23	0.818	0.69	1.61
IED	-0.01	1.01	-0.05	1.03	1.18	0.21	0.93	0.350	0.83	1.66
SST	0.07	1.30	0.11	1.16	1.21	0.21	1.10	0.269	0.86	1.71
RVP	-0.75	1.04	0.01	1.00	1.35	0.15	2.65	0.007	1.08	1.68

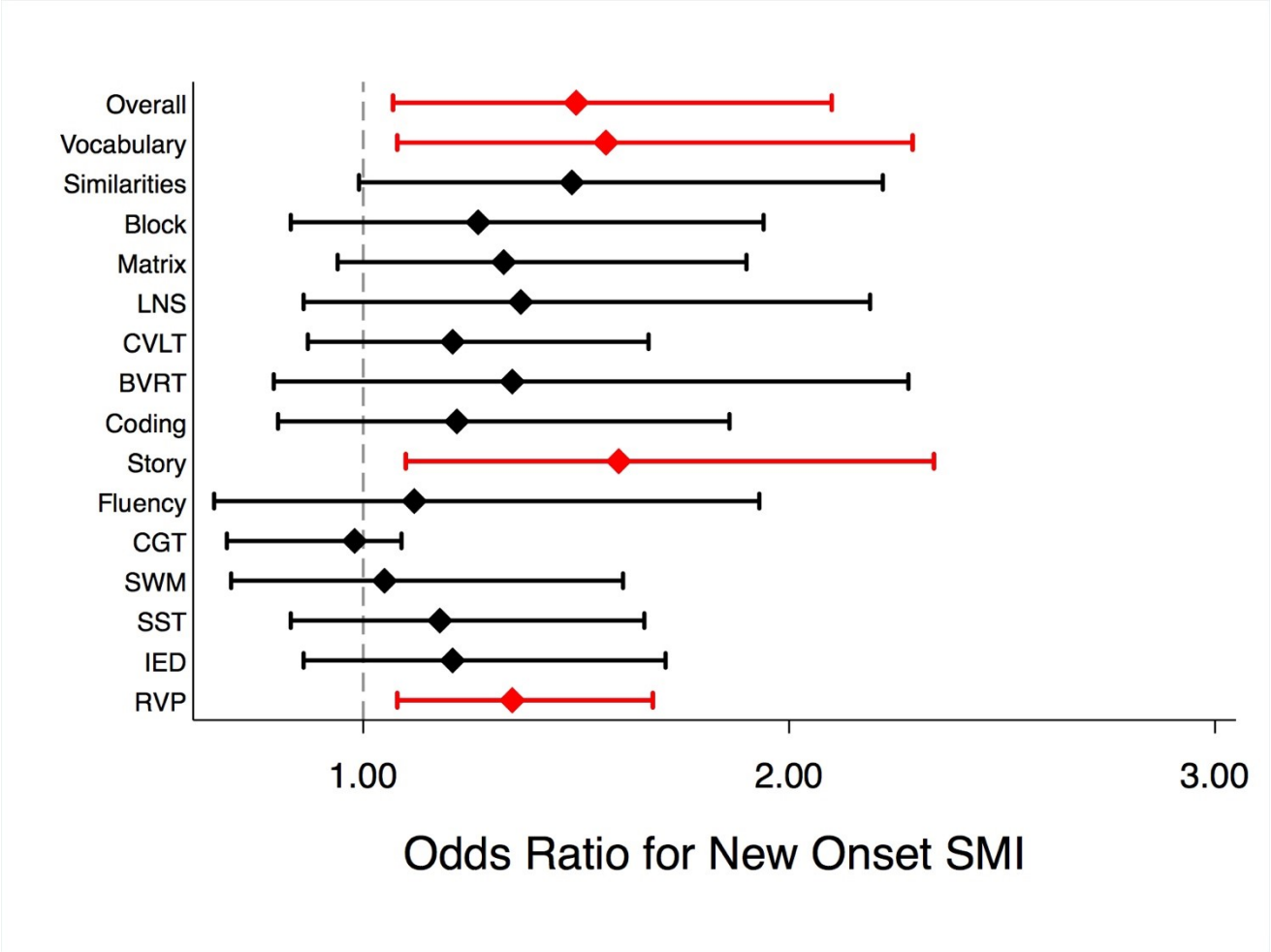
Note. **N=309.** SE = Standard Error, 95% CI = 95% Confidence Interval, Overall = Overall cognition, Matrix = Matrix Reasoning, LNS = Letter Number Sequencing, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, Coding = Digit Symbol Coding, Story = Story Memory, Fluency = Verbal Fluency, CGT = Cambridge Gambling Task, SWM=Spatial working memory, IED = Intra/Extra Dimensional Set Shifting, SST = Signal Stop Task, RVP = Rapid Visual Processing Task.

Table 5.3 *Sensitivity analyses probing the effect of sample characteristics on the association between worse overall cognitive performance and onset of severe mental illness*

Sensitivity Analysis	Odds Ratio	SE	p-value	95% CI Lower	95% CI Upper
Cannabis use	1.40	0.22	0.034	1.03	1.92
Socioeconomic Status	1.42	0.25	0.047	1.14	1.35
ADHD	1.49	0.26	0.019	1.06	2.09
Anxiety Disorders	1.52	0.24	0.013	1.09	2.10

Note. **N = 309.** Attention Deficit/ Hyperactivity Disorder, SE = Standard Error, 95% CI = 95% Confidence Interval.

Figure 5.1. Performance on cognitive tests and onset of severe mental illness (SMI)



Note. N=309. Overall = Overall cognitive performance, Block = Block Design, Matrix = Matrix Reasoning, LNS = Letter Number Sequencing, CVLT = California Verbal Learning Test, BVRT = Benton Visual Retention Test, Coding = Digit Symbol Coding, Story = Story Memory, Fluency = Verbal Fluency, CGT = Cambridge Gambling Task, SWM=Spatial working memory, SST = Signal Stop Task, IED = Intra/Extra Dimensional Set Shifting, RVP = Rapid Visual Processing Task. Error bars represent the lower and upper bound of the 95% CI for the Odds Ratio. Results shown in red indicate are nominally significant (p<.05). Error bars represent the lower and upper bound of the 95% CI for the Odds Ratio.

We found no association between the cognitive performance and onset of SMI in the following cognitive domains: performance IQ (including Block Design and Matrix Reasoning subtests), verbal working memory (Letter Number Sequencing), verbal learning and memory (California Verbal Learning Test), visual memory (Benton Visual Retention Test), processing speed (Digit Symbol Coding subtest), verbal fluency (Delis Kaplan Executive Functioning System), decision-making (Cambridge Gambling Task), visual working memory (Spatial Working Memory), set shifting (Intra/Extra Dimensional Set Shifting), and inhibition (Stop Signal Task) ($p > 0.05$).

5.5 Discussion

In a longitudinal sample of offspring at familial risk for SMI, we found a robust association between lower overall cognitive performance and onset of an SMI diagnosis. Findings remained significant after controlling for age, sex, clustering within families, cannabis use, socioeconomic status, and offspring lifetime diagnosis of ADHD and anxiety disorders. Several individual cognitive domains were nominally significant ($p<.05$) in predicting new onset SMI, including vocabulary, story memory, and sustained attention. No individual cognitive domain was statistically significant after controlling for multiple comparisons, however.

Our findings are consistent with several large population-based birth cohort studies, indicating that lower IQ in childhood and adolescence predicts onset of psychotic SMI by adulthood. Prior research in this field has typically investigated FSIQ as a predictor of SMI onset, rather than a wide range of cognitive tasks. Cannon et al., found that impairments in cognitive performance, motor skills, language, emotional and interpersonal development assessed at ages 5, 7, 9 and 11 were associated with the development of schizophreniform disorder by age 26. In line with these findings, in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, participants who went on to develop psychotic disorder showed increasing cognitive deficits at 18 months, 4 years, 8 years, 15 years, and 20 years of age (Mollon et al., 2018). Our findings are also consistent with clinical high-risk samples. Simon et al. (2012) found that individuals who went on to develop psychosis over a 2-year follow-up period showed deficits in global cognition at baseline.

In contrast to our findings, several large, prospective birth cohort studies found no association between cognitive performance in childhood and adolescence and onset of non-psychotic SMI in adulthood. Although Cannon et al. (2002) found that lower childhood IQ predicted schizophreniform disorder by age 26, they observed no association between cognitive performance and later development of diagnosable mania and depressive disorders. In a follow-up analysis also within the Dunedin cohort, J.D. Schaefer et al. (2017) found no association between performance on two IQ tasks of the Wechsler Intelligence Scale for Children (Matrix Reasoning and Information) assessed at age 12 and the onset of major depressive disorder at age 38 in a large, general-population birth cohort study. Differences in findings may be due to the familial risk design of this study and the wider range of cognitive tests administered in our study. In sum, these findings replicate evidence supporting a neurodevelopmental basis to the development of SMI.

One of the largest effect sizes was observed between poorer performance on story memory and onset of SMI. Deficits in story memory have been reported across SMIs (Aleman et al., 1999; Bora et al., 2013; Kurtz & Gerraty, 2009; Martinez-Aran et al., 2004; Simonsen et al., 2011; Smith, Barch, & Csernansky, 2009). Impairments in story memory have also been shown in first-degree relatives of bipolar disorder and schizophrenia (Balanza-Martinez et al., 2008; Snitz et al., 2006). Based on our recent meta-analysis including of 54 non-overlapping samples of cognitive performance in first-degree relatives of major depressive disorder, story memory has not yet been investigated in this population (MacKenzie et al., 2019). In the aforementioned North American Prodrome Longitudinal Study (NAPLS), Seidman et al. (2016) found that verbal and

declarative memory was the strongest predictor of onset of psychosis in the largest multi-site cohort of individuals at clinical high risk. Findings remained after controlling for IQ, medication, alcohol and cannabis use. In line with these findings, Cornblatt et al. (2015) found that verbal memory predicted onset of psychotic disorder in a 5 year longitudinal follow-up of adolescents and young adults at clinical high risk.

It is notable that prior investigation has found that impairment in verbal memory (composite of story memory and the California Verbal Learning Test) performance predicts poor functional outcomes in a longitudinal study of youth at clinical high risk for psychosis, with an effect size remarkably similar to the one observed in the present sample (OR = 1.74, 95% CI 1.69 to 2.59, p =0.006) (Carrion et al., 2013). In addition, normal verbal memory performance uniquely predicted remission from clinical high risk status with a predictive value of 82% (Simon et al., 2012). Our results found that deficits in story memory were nominally associated with later development of offspring SMI in individuals at familial risk. Impairments were specific to story memory assessed with the Children's Memory Scale and Wechsler Memory Scale. We observed no association between verbal learning and memory assessed with the California Verbal Learning Test and onset of SMI in offspring at familial risk. The association between story memory and offspring onset of SMI was not significant after correction for multiple comparison. However, our findings may be impacted by the small sample size of offspring who developed SMI upon follow-up. These findings highlight the potential role of story memory in informing the design of early interventions in those at familial risk.

5.5.1. Implications

The data presented have implications for early intervention and prevention of SMI in those at familial risk. Early interventions could be targeted to improve cognitive abilities in individuals at familial risk. Bechdolf et al. (2012) provided an integrated intervention for individuals meeting criteria for early initial prodromal state (EIPS) for psychosis, including cognitive behavioural therapy, social skills training, cognitive remediation (computer-based training of concentration, attention, vigilance and memory), and psychoeducation for families compared with supportive counselling. The authors found reduced conversion rates and longer time to psychosis diagnosis in the integrated treatment group compared with the supportive counselling group. However, due to the integrated treatment design, it was not possible to determine the unique contribution of cognitive remediation intervention as a potential preventative intervention in the development of psychosis.

Early interventions may also target cognitive development in early childhood prior to the onset of psychopathology. Singla et al. (2015) completed a randomized controlled trial parenting intervention (increasing parent-child interaction through play and talk, and maternal well-being) in mothers with MDD and their children younger than age 3. Post intervention follow-up findings indicated improved cognitive and language abilities in offspring as well as reduced maternal depressive symptoms in the intervention group (Singla et al., 2015). To our knowledge, there are currently no data on the effect of early interventions aimed at cognitive remediation on long-term prevalence rates of SMI and the social and occupational impact of these disorders in those at familial risk. Longitudinal intervention research is needed to investigate the impact of early interventions targeting cognitive development in those at familial risk for SMI.

5.5.2 Strengths and Limitations

Our findings should be interpreted in the context of several limitations. First, the sample size of the offspring SMI group was not large. This may have limited statistical power to detect significant findings in cognitive domains after Bonferroni correction. This was particularly noticeable in the relationship between story memory and onset of SMI, which was the largest effect size but did not remain significant after controlling for multiple comparisons. However, the finding of worse overall cognitive performance and onset of SMI was robust to correction for the effects of age, sex, familial clustering, socioeconomic status, cannabis use and lifetime diagnoses of ADHD and anxiety disorders. Second, the participants have not completely passed through the developmental period for typical onset of SMI. Therefore, we cannot rule out the possibility that larger effects between worse cognitive performance and later onset of SMI would be observed if additional onsets of offspring SMI occur upon longitudinal follow-up. However, the effect sizes observed in this sample were similar to findings in large, population-based birth cohorts (Cannon et al., 2002). Third, although our study was sufficiently powered to detect moderate effect sizes in story memory and sustained attention, it may have been underpowered to detect milder impairment that may reflect a weaker association between cognitive performance and onset of severe mental illness.

5.5.3 Future directions

To investigate whether early intervention targeted at cognitive development would modify progression, prognosis, or potentially prevent onset of SMI, longitudinal randomized controlled trials are needed. Longitudinal studies should include follow-up through the typical onset period (adolescence through early adulthood).

5.5.4 Conclusion

In conclusion, the present findings indicate that mild-to-moderate impairment in overall cognitive performance predicted onset of SMI diagnosis in a longitudinal cohort of individuals at familial risk. At the level of specific cognitive domains, the association was specific to vocabulary, story memory, and sustained attention.

CHAPTER 6

GENERAL DISCUSSION

6.1 Summary of findings

In study 1, we found that lower cognitive ability is a feature of neurodevelopmental vulnerability to SMI, rather than a manifestation of disorder burden or treatment. Sons and daughters of parents with non-psychotic SMI performed significantly worse than controls on several cognitive tests, including verbal intelligence, visual memory, and decision-making. However none of these differences were significant after correction for multiple comparison. Offspring of parents with psychotic SMI exhibited a larger range of cognitive deficits in overall cognition, verbal working memory, processing speed, verbal learning and memory, verbal fluency, and sustained attention compared with controls. The association between offspring overall cognition and parent diagnosis of psychotic SMI was independent of socioeconomic status, and offspring lifetime diagnosis of attention deficit/hyperactivity disorder and anxiety disorders.

In study 2, we found that worse overall cognitive performance was associated with propensity to experience psychotic symptoms in a model adjusting for age, sex, and clustering within families. Findings remained significant after controlling for socioeconomic status, cannabis use, hot executive function, and offspring lifetime diagnosis of ADHD and anxiety disorders. Impairments in 6 of 15 cognitive domains was nominally associated with psychotic symptoms, including verbal IQ, visual memory, hot executive function, spatial working memory, and set shifting. However no individual cognitive domain was statistically significant after correction for multiple comparison. We found no association between performance IQ, verbal working memory, verbal learning and memory, processing speed, verbal fluency cognitive inhibition, and

sustained attention. These findings indicate that deficits in overall cognitive performance may be an important neurodevelopmental indicator of risk to later onset of severe mental illness.

In study 3, we examined cognitive data across a 6-year longitudinal sample (mean number of assessments completed per participant 2.73) of sons and daughters of parents affected with SMI. We found that worse performance on a composite measure of overall cognitive performance was associated with offspring new onset of SMI diagnoses upon follow-up. Findings remained after controlling for age, sex, familial clustering, cannabis use, socioeconomic status, and offspring lifetime diagnoses of ADHD and anxiety disorders. In addition, worse performance on several cognitive domains was nominally associated with onset of offspring severe mental illness (p <.05), including verbal IQ, story memory, and sustained attention. However, these associations did not survive correction for multiple comparisons.

These findings indicate that worse performance on overall cognition is associated with familial risk for psychotic SMI, propensity to experience psychotic symptoms, and new onsets of offspring SMI diagnoses. The finding of impairment in premorbid cognitive performance and onset of psychotic disorder is consistent with several large, prospective population-based studies (Cannon et al., 2002; Jones et al., 1994; Mollon et al., 2018; Osler et al., 2007). Only one other study compared cognitive performance in childhood and associations to both psychotic symptoms and new onset SMI (Cannon, 2002). In line with our findings, Cannon et al. (2002) found that deficits in IQ (composite of IQ tests administered at age 3, 5, 7, 9, and 11 years) were predictive of later development of strong and not weak psychotic symptoms (similar to the consesnsus rated

definite psychotic symptoms in this thesis) as self-reported by participants at age 11, and of schizophreniform disorder by age 26. Our results extend these findings to show that impairment in overall cognition is assoiciated with risk for later development of transdiagnostic SMI (including major mood and psychotic disorders).

Worse performance on verbal IQ was more strongly associated with familial risk, psychotic symptoms, and onset of SMI across studies when compared with performance IQ subtests. These findings may be impacted by the early development of language. Previous research indicates that mothers diagnosed with major depressive disorder show decreased shared attention and vocalization with their infants and toddlers and that children of mothers with MDD speak less often to their mothers compared with controls (Breznitz & Sherman, 1987; Bettes, 1988; Field, Healy, Goldstein, & Guthertz, 1990; Goldsmith & Rogoff, 1997; Porritt, Zinser, Bachorowski, & Kaplan, 2014), which may negatively impact verbal cognitive development in children.

The present findings of relatively worse performance on verbal IQ tests compared with performance IQ tests is consistent with a large, population-based prospective cohort in Sweden (National Patient Regiter later linked with the Swedish Conscription Register), which found that a relative decline in verbal cognition between 13 and 18 years of age predicted onset of schizophrenia, schizoaffective disorder, and other nonaffective psychoses (MacCabe et al., 2013). They found no association between decline in spatial or inductive cognition and later onset of psychotic disorder. This is also consistent with the findings of verbal cognitive performance as a specific predictor of psychotic symptoms. Koike et al. (2018) found that lower verbal cognitive ability at age 8 and developmental lag (gradually worsening performance between assessment at 8 years and

follow-up assessment at 15 years of age) was predictive of psychotic symptoms at age 53. In sum, deficits in verbal IQ are common to both familial and clinical risk for SMI and are associated with onset of offspring SMI diagnoses within longitudinal follow-up. The present findings indicate a potential specificity in the relationship between verbal cognition and familial and clinical risk for severe mental illness. This highlights the importance of utilizing a wide range of cognitive tests to investigate the specific cognitive risk factors underlying etiology of the development of severe mental illness.

6.2. Future Directions

The findings in this thesis have implications for early intervention. In individuals with psychotic disorder, neurocognitive deficits have greater impact on long-term functioning than negative and positive symptoms of psychosis (Green, 1996). This highlights the importance of future interventions targeted toward cognition within individuals at familial and clinical risk for severe mental illness. In a recent systematic review by Glenthoj et al. (2017), six studies investigated the effect of cognitive remediation in individuals at clinical high risk for psychosis. Four of the five studies that investigated cognitive performance found improvements on post-intervention cognitive tests. Two of the four studies that investigated functional outcome found improvement in social functioning. However, only one study examined a cognitive remediation intervention and associations with later onset of psychosis in individuals at clinical risk (Bechdolf et al., 2012). The combined intervention included cognitive behavioural therapy, social skills training, cognitive remediation (consisting of computer-based training programs to target concentration, attention, vigilance and memory), and psychoeducation for families compared with a supportive counselling intervention. At 12

and 24-month follow-up, reduced rates of conversion and longer time in onset of psychotic disorder were found within the integrated treatment group compared with the supportive counselling group. However, it was not possible to determine the specific effects of the cognitive remediation due to the integrated intervention design.

With regard to the deficits in executive function and association with psychotic symptoms found in study 2, evidence indicates that it is possible to remediate executive functions in childhood through early interventions, including traditional martial arts, specific school curricula, mindfulness, yoga and computerized training (Diamond, 2012; Diamond & Lee, 2011). The strongest improvements were found in programs that integrate physical activity, character development (e.g., traditional martial arts), and challenge executive functions. Diamond (2012) hypothesizes that the route to improving executive function in childhood includes increasing joy, social belonging and support, confidence, pride, sense of self-efficacy, and physical fitness.

Psychological intervention targeted toward the parent-child relationship has also been shown to be protective for early cognitive development. Singla, Kumbakumba, & Aboud (2015) completed a randomized controlled trial targeted to increasing healthy parent-child interaction through play and talk as well as coping strategies for maternal wellbeing. The authors found improved cognitive and language abilities in children as well as reduced maternal depressive symptoms. In line with these findings, Cicchetti et al. (2000) randomized mothers with major depressive disorder and their children to three groups: (1) Toddler-Parent Psychotherapy group, (2) Non-intervention group of mothers with major depressive disorder and their children, and (3) Control group of mothers with no lifetime diagnosis of mental disorder. At follow-up, the authors found a decline in IQ

in the children randomized to the non-intervention group. The largest differences in cognitive ability were found in the children of mothers who experienced recurrent depressive episodes and did not receive Toddler-Parent Psychotherapy. In relation to the consistent verbal IQ findings within this thesis, it is interesting to note that the relative decline in functioning was specific to verbal IQ rather than performance IQ.

There are currently no data on the effect of early interventions aimed at cognitive remediation on long-term prevalence rates of SMI in those at familial risk. Longitudinal intervention research is needed to investigate the impact of early interventions targeting cognitive development in first-degree relatives of individuals with SMI.

Recent updates to the neurodevelopmental theory of schizophrenia highlight the potential for neurodegenerative processes throughout childhood and adolescence which may contribute to the risk for psychotic disorder by early adulthood (J. J. McGrath et al., 2009). This is consistent with findings from general population cohort studies. In the Copenhagen Perinatal Cohort, gradual decline in cognitive performance between age 12 and age 18 was associated with the development of schizophrenia in adulthood (Osler et al., 2007). It is not currently known whether progressive decline in cognitive function is associated with the onset of severe mood and psychotic disorders in those at familial risk. The FORBOW study is a longitudinal cohort enriched for familial risk for SMI and cognitive assessments will be ongoing during follow-up assessments. In future analyses, we are aiming to investigate whether relative decline and changes in cognitive ability increases risk of onset of psychotic symptoms and SMI diagnoses in future analyses.

6.3 Conclusions

In conclusion, we identified that cognitive performance is an important neurodevelopmental indicator of risk in those at familial and clinical risk for severe mental illness. We found that overall cognitive performance is associated with familial risk for SMI, propensity to experience psychotic symptoms, and onset of offspring severe mental illness diagnosis. These findings are novel and will contribute to the design and implementation of early intervention for those at familial and clinical risk for severe mental illnesses. To investigate whether interventions targeting cognition in individuals at familial risk for SMI improves long-term prognosis and functioning or reduces prevalence rates of onset, further longitudinal research is needed.

BIBLIOGRAPHY

Agnew-Blais, J., & Seidman, L. J. (2013). Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: a quantitative and qualitative review. *Cognitive Neuropsychiatry, 18*(1-2), 44-82. doi:10.1080/13546805.2012.676309

Aleman, A., Hijman, R., de Haan, E. H. F., & Kahn, R. S. (1999). Memory impairment in schizophrenia: A meta-analysis. *American Journal of Psychiatry, 156*, 1358-1366. doi:10.1176/ajp.156.9.1358

Arsenault, L., Cannon, M., Fisher, H.L., Polanczyk, G., Moffit, T.E., Caspi, A. (2011). Childhood trauma and children's emerging psychotic symptoms : A genetically sensitive longitudinal cohort study. *American Journal of Psychiatry, 168*, 65-72. doi:10.1016/j.pestbp.2011.02.012.Investigations

Arts, B., Jabben N., Krabbendam, L., van Os J. (2007). Meta-analyses of cognitive function in euthymic bipolar patients and their first-degree relatives. *Psychological Medicine, 38*(6), 771-685.

Aydin, E., Cansu Ulgen, M., Tabo, A., Devrim Balaban, O., Yesilyurt, S., & Yumrukcal, H. (2017). Executive function and genetic loading in nonpsychotic relatives of schizophrenia patients. *Psychiatry Research, 248*, 105-110. doi:10.1016/j.psychres.2016.12.027

Balanza-Martinez, V., Rubio, C., Selva-Vera, G., Martinez-Aran, A., Sanchez-Moreno, J., Salazar-Fraile, J., . . . Tabares-Seisdedos, R. (2008). Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar

disorder subjects: a systematic review. *Neuroscience Biobehavioral Reviews, 32*(8), 1426-1438. doi:10.1016/j.neubiorev.2008.05.019

Bartels-Velthuis, A. A., van de Willige, G., Jenner, J. A., van Os, J., & Wiersma, D. (2011). Course of auditory vocal hallucinations in childhood: 5-year follow-up study. *British Journal of Psychiatry, 199*(4), 296-302. doi:10.1192/bjp.bp.110.086918

Bauer, I. E., Wu, M. J., Frazier, T. W., Mwangi, B., Spiker, D., Zunta-Soares, G. B., & Soares, J. C. (2016). Neurocognitive functioning in individuals with bipolar disorder and their healthy siblings: A preliminary study. *Journal of Affective Disorders, 201*, 51-56. doi:10.1016/j.jad.2016.04.026

Bechara, A. (2004). The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. *Brain and Cognition, 55*, 30-40. doi:10.1016/j.bandc.2003.04.001

Bechdolf, A., Wagner, M., Ruhrmann, S., Harrigan, S., Putzfeld, V., Pukrop, R., . . . Klosterkotter, J. (2012). Preventing progression to first-episode psychosis in early initial prodromal states. *British Journal of Psychiatry, 200*(1), 22-29. doi:10.1192/bjp.bp.109.066357

Benton, A. L. (1974). *Benton Visual Retention Test-Clinical and Experimental Applications*. San Antonio, TX: Psychological Corporation.

Bettes, B. A. (1988). Maternal depression and motherese: Temporal and intonational features. *Child Development*, 59: 1089-1096.

Bevan Jones, R., Mars, B., Collishaw, S., Potter, R., Thapar, A., Craddock, N., . . . Zammit, S. (2016). Prevalence and correlates of psychotic experiences amongst

children of depressed parents. *Psychiatry Research, 243*, 81-86. doi:10.1016/j.psychres.2016.03.012

Blanchard, M. M., Jacobson, S., Clarke, M. C., Connor, D., Kelleher, I., Garavan, H., . . . Cannon, M. (2010). Language, motor and speed of processing deficits in adolescents with subclinical psychotic symptoms. *Schizophrenia Research, 123*, 71-76. doi:10.1016/j.schres.2010.05.028

Bora, E. (2015). Neurodevelopmental origin of cognitive impairment in schizophrenia. *Psychological Medicine, 45*(1), 1-9. doi:10.1017/S0033291714001263

Bora, E. (2017). A comparative meta-analysis of neurocognition in first-degree relatives of patients with schizophrenia and bipolar disorder. *European Psychiatry, 45*, 121-128. doi:10.1016/j.eurpsy.2017.06.003

Bora, E., Harrison, B. J., Yücel, M., & Pantelis, C. (2013). Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychological Medicine, 43*, 2017-2026. doi:10.1017/S0033291712002085

Bora, E., & Ozerdem, A. (2017). A meta-analysis of neurocognition in youth with familial high risk for bipolar disorder. *European Psychiatry, 44*, 17-23. doi:10.1016/j.eurpsy.2017.02.483

Bora, E., & Ozerdem, A. (2017). Social cognition in first-degree relatives of patients with bipolar disorder: A meta-analysis. *European Neuropsychopharmacology, 27*(4), 293-300. doi:10.1016/j.euroneuro.2017.02.009

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and

their first-degree relatives. *Journal of Affective Disorders, 113*, 1-20. doi:10.1016/j.jad.2008.06.009

Brasso, M., & Bornstein, R. (1999). Neuropsychological deficits in psychotic versus nonpsychotic unipolar depression. *Neuropsychology, 13*, 69-75.

Calafiore, D., Rossell, S. L., & Van Rheenen, T. E. (2018). Cognitive abilities in first-degree relatives of individuals with bipolar disorder. *Journal of Affective Disorders, 225*, 147-152. doi:10.1016/j.jad.2017.08.029

Caldiroli, A., Buoli, M., Serati, M., Cahn, W., & Altamura, A. C. (2016). General and social cognition in remitted first-episode schizophrenia patients: a comparative study. *European Archives of Psychiatry and Clinical Neuroscience, 266*(7), 639-647. doi:10.1007/s00406-016-0701-x

Cannon, M., Caspi, A., Moffi, T. E., Harrington, H., Taylor, A., Murray, R., & Poulton, R. (2002). Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder. *Archives of General Psychiatry, 59*, 449-456.

Carrion, R. E., McLaughlin, D., Goldberg, T. E., Auther, A. M., Olsen, R. H., Olvet, D. M., . . . Cornblatt, B. A. (2013). Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA Psychiatry, 70*(11), 1133-1142. doi:10.1001/jamapsychiatry.2013.1909

Christensen, M. V., Kyvik, K. O., & Kessing, L. V. (2006). Cognitive function in unaffected twins discordant for affective disorder. *Psychological Medicine, 36*, 1119-1129. doi:10.1017/S0033291706007896

Cicchetti, D., Rogosch, F. A., & Toth, S. L. (2000). The efficacy of Toddler-Parent Psychotherapy for fostering cognitive development in offspring of depressed

mothers. *Journal of Abnormal Child Psychology, 28*, 135-148. doi:10.1023/A:1005118713814

Cohen, M. (1997). *Children's Memory Scale*. San Antonio, TX: Psychological Corporation.

Cornblatt, B. A., Carrion, R. E., Auther, A., McLaughlin, D., Olsen, R. H., John, M., & Correll, C. U. (2015). Psychosis prevention: A modified clinical high risk perspective from the recognition and prevention (RAP) program. *American Journal of Psychiatry, 172*(10), 986-994. doi:10.1176/appi.ajp.2015.13121686

Cullen, A. E., Dickson, H., West, S. A., Morris, R. G., Mould, G. L., Hodgins, S., . . . Laurens, K. R. (2010). Neurocognitive performance in children aged 9-12years who present putative antecedents of schizophrenia. *Schizophrenia Research, 121*, 15-23. doi:10.1016/j.schres.2010.05.034

Cuthbert, B. N., & Insel, T. R. (2010). Toward new approaches to psychotic disorders: The NIMH research domain criteria project. *Schizophrenia Bulletin, 36*, 1061-1062. doi:10.1093/schbul/sbq108

De Herdt, A., Wampers, M., Vancampfort, D., De Hert, M., Vanhees, L., Demunter, H., . . . Probst, M. (2013). Neurocognition in clinical high risk young adults who did or did not convert to a first schizophrenic psychosis: A meta-analysis. *Schizophrenia Research, 149*, 48-55. doi:10.1016/j.schres.2013.06.017

De Hert, M., Correll, C. U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., . . . Leucht, S. (2011). Physical illness in patients with severe mental disorders I. Prevalence, impact of medications and disparities in health care. *World Psychiatry, 10*, 52-77.

de la Serna, E., Sugranyes, G., Sanchez-Gistau, V., Rodriguez-Toscano, E., Baeza, I., Vila, M., . . . Castro-Fornieles, J. (2017). Neuropsychological characteristics of child and adolescent offspring of patients with schizophrenia or bipolar disorder. *Schizophr Research, 183*, 110-115. doi:10.1016/j.schres.2016.11.007

Delis, D. C. (2000). *California Verbal Learning Test* (Second ed.). San Antonio, TX: Psychological Corporation.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001a). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1994). *California Verbal Learning Test, Children's Version* (Second ed.). San Antonio, TX: Psychological Corporation.

Diagnostic and Statistical Manual of Mental Disorders (DSM-5). (5th ed.). Arlington, VA: American Psychiatric Publishing.

Diamond, A. (2012). Activities and programs that improve children's executive functions. *Current Directions in Psychological Science, 21*(5), 335-341. doi:10.1177/0963721412453722

Diamond, A., & Lee, K. (2011). Interventions shown to aid executive function development in children 4 to 12 years old. *Science, 333*, 959-964. doi:10.1126/science.1204529

Dickson, H., Cullen, A. E., Reichenberg, A., Hodgins, S., Campbell, D. D., Morris, R. G., & Laurens, K. R. (2014). Cognitive impairment among children at-risk for schizophrenia. *Journal of Psychiatric Research, 50*, 92-99. doi:10.1016/j.jpsychires.2013.12.003

Drake, R., & Whitely, R. (2014). Recovery and severe mental illness: Description and analysis. *The Canadian Journal of Psychiatry, 59*, 236-242.

Eack, S. M., Hogarty, G. E., Cho, R. Y., Prasad, K. M., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2011). Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia. *Clinical and Translational Science, 4*, 105. doi:10.1111/j.1752-8062.2011.00269.x

Eack, S. M., Hogarty, G. E., Greenwald, D. P., Hogarty, S. S., & Keshavan, M. S. (2007). Cognitive enhancement therapy improves emotional intelligence in early course schizophrenia: preliminary effects. *Schizophrenia Research, 89*(1-3), 308-311. doi:10.1016/j.schres.2006.08.018

Endicott, J., Spitzer, R. L. (1978). A diagnostic interview: the schedule for affective disorders and schizophrenia. *JAMA Psychiatry, 35*, 873-843.

Fernandez, V. G., Asarnow, R., Narr, K. L., Subotnik, K. L., Kuppinger, H., Fogelson, D., & Nuechterlein, K. H. (2018). Temporal lobe thickness and verbal memory in first-degree relatives of individuals with schizophrenia. *Schizophr Research, 199*, 221-225. doi:10.1016/j.schres.2018.02.038

Field, T., Healy, B. T., Goldstein, S., Guthertz, M. (1990). Behavior-state matching and synchrony in mother-infant interactions of nondepressed versus depressed dyads. *Developmental Psychology*, 26: 7-14.

First, M. B., Williams, J. B. W., Spitzer, R. L. (2015). Structured Clinical Interview for DSM-5, Research Version.

Fonville, L., Kadosh, K. C., Drakesmith, M., Dutt, A., Zammit, S., Mollon, J., . . . David, A. S. (2015). Psychotic experiences, working memory, and the developing brain:

A multimodal neuroimaging study. *Cerebral Cortex, 25*, 4828-4838. doi:10.1093/cercor/bhv181

Frajo-Apor, B., Kemmler, G., Pardeller, S., Huber, M., Macina, C., Welte, A. S., & Hofer, A. (2017). Is emotional intelligence impaired in unaffected siblings of patients with schizophrenia? *Journal of the International Neuropsychological Society, 23*(7), 577-583. doi:10.1017/S135561771700042X

Frith, C. D. (2008). Social cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences, 363*(1499), 2033-2039. doi:10.1098/rstb.2008.0005

Fux, L., Walger, P., Schimmelmann, B. G., & Schultze-Lutter, F. (2013). The schizophrenia proneness instrument, child and youth version (SPI-CY): Practicability and discriminative validity. *Schizophrenia Research, 146*, 69-78. doi:10.1016/j.schres.2013.02.014

Giakoumaki, S. G., Roussos, P., Pallis, E. G., & Bitsios, P. (2011). Sustained attention and working memory deficits follow a familial pattern in schizophrenia. *Archives of Clinical Neuropsychology, 26*(7), 687-695. doi:10.1093/arclin/acr060

Glenthoj, L. B., Hjorthoj, C., Kristensen, T. D., Davidson, C. A., Nordentoft, M. (2017). The effect of cognitive remediation in individuals at ultra-high risk for psychosis: A systematic review. *Npj Schizophrenia*, 3: 20-28

Goldsmith, D. F., Rogoff, B. (1997). Mothers' and toddlers' coordinated joint focus of attention: Variations with maternal dysphoric symptoms. *Developmental Psychology*, 33: 113-119.

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? . *American Journal of Psychiatry, 153*(3), 321-330.

Gur, R. E., Nimgaonkar V. L., Almasy, L., Calkins, M. E., Ragland, J. D., Pogue-Geile, M. F., Kanes, S., Blangero, J., Gur, R. C. (2007). Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *American Journal of Psychiatry, 164*(5), 813-819.

Hanssen, M., Peeters, F., Krabbendam, L., Radstake, S., Verdoux, H., van Os, J. (2003). How psychotic are individuals with non-psychotic disorders? *Social Psychiatry and Epidemiology, 38*(3), 149-154.

Hay, D. F., Pawlby, S., Sharp, D., Asten, P., Mills, A., & Kumar, R. (2001). Intellectual problems shown by 11-year-old children whose mothers had postnatal depression. *Journal of Child Psychology and Psychiatry, 42*, 871-889. doi:10.1111/1469-7610.00784

Hemager, N., Plessen, K. J., Thorup, A., Christiani, C., Ellersgaard, D., Spang, K. S., . . . Jepsen, J. R. M. (2018). Assessment of neurocognitive functions in 7-year-old children at familial high risk for schizophrenia or bipolar disorder: The danish high risk and resilience study VIA 7. *JAMA Psychiatry, 75*(8), 844-852. doi:10.1001/jamapsychiatry.2018.1415

Hoehne, A., Richard-Devantoy, S., Ding, Y., Turecki, G., & Jollant, F. (2015). First-degree relatives of suicide completers may have impaired decision-making but functional cognitive control. *Journal of Psychiatric Research, 68*, 192-197. doi:10.1016/j.jpsychires.2015.07.004

Horton, L. E., Bridgwater, M. A., & Haas, G. L. (2017). Emotion recognition and social skills in child and adolescent offspring of parents with schizophrenia. *Cognitive Neuropsychiatry, 22*(3), 175-185. doi:10.1080/13546805.2017.1297223

Hou, C.-L., Xiang, Y.-T., Wang, Z.-L., Everall, I., Tang, Y., Yang, C., . . . Jia, F.-J. (2016). Cognitive functioning in individuals at ultra-high risk for psychosis, first-degree relatives of patients with psychosis and patients with first-episode schizophrenia. *Schizophrenia Research, 174*, 71-76. doi:10.1016/j.schres.2016.04.034

Jameson, K. G., Nasrallah, H. A., Northern, T. G., & Welge, J. A. (2011). Executive function impairment in first-degree relatives of persons with schizophrenia: A meta-analysis of controlled studies. *Asian Journal of Psychiatry, 4*, 96-99. doi:10.1016/j.ajp.2011.04.001

Jeppesen, P., Larsen, J. T., Clemmensen, L., Munkholm, A., Rimvall, M. K., Rask, C. U., . . . Skovgaard, A. M. (2015). The CCC2000 birth cohort study of register-based family history of mental disorders and psychotic experiences in offspring. *Schizophrenia Bulletin, 41*(5), 1084-1094. doi:10.1093/schbul/sbu167

Jimenez-Lopez, E., Aparicio, A. I., Sanchez-Morla, E. M., Rodriguez-Jimenez, R., Vieta, E., & Santos, J. L. (2017). Neurocognition in patients with psychotic and non-psychotic bipolar I disorder. A comparative study with individuals with schizophrenia. *Journal of Affective Disorders, 222*, 169-176. doi:10.1016/j.jad.2017.07.014

Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *The Lancet, 344*, 1398-1402.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. D. (1997). Schedule for affective disorders and schizophrenia for school-age

children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 980-988. doi:10.1097/00004583-199707000-00021

Keck, P. E., McElroy, S. L., Havens, J. R., Altshuler L. L., Nolen, W. A., Frye, M. A., Suppes T., Denicoff, K. D., Kupka, R., Leverich, G. S., Rush, A. J., Post, R. M. . (2003). Psychosis in bipolar disorder: Phenomenology and impact on morbidity and course of illness. *Comprehensive Psychiatry, 44*(4), 263-269.

Kelleher, I., Clarke, M. C., Rawdon, C., Murphy, J., & Cannon, M. (2013). Neurocognition in the extended psychosis phenotype: performance of a community sample of adolescents with psychotic symptoms on the MATRICS neurocognitive battery. *Schizophrenia Bulletin, 39*(5), 1018-1026. doi:10.1093/schbul/sbs086

Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., . . . Cannon, M. (2012). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *British Journal of Psychiatry, 201*(1), 26-32. doi:10.1192/bjp.bp.111.101543

Kelleher, I., Murtagh, A., Clarke, M. C., Murphy, J., Rawdon, C., & Cannon, M. (2012). Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: Support for the processing speed hypothesis. *Cognitive Neuropsychiatry, 18*, 1-17. doi:10.1080/13546805.2012.682363

Keshavan, M. S., Kulkarni, S., Bhojraj, T., Francis, A., Diwadkar, V., Montrose, D. M., . . . Sweeney, J. (2010). Premorbid cognitive deficits in young relatives of

schizophrenia patients. *Frontiers in Human Neuroscience, 3*, 62. doi:10.3389/neuro.09.062.2009

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*, 593-602. doi:10.1001/archpsyc.62.6.593

Kessler, R. C., Berglund, P. A., Bruce, M. L. (2001). The prevalence and correlates of untreated serious mental illness. *Health Services Research, 36*(6), 987-1007.

Klimes-Dougan, B., Ronsaville, D., Wiggs, E. A., & Martinez, P. E. (2006). Neuropsychological functioning in adolescent children of mothers with a history of bipolar or major depressive disorders. *Biological Psychiatry, 60*, 957-965. doi:10.1016/j.biopsych.2006.03.031

Koenen, K. C., Moffitt, T. E., Roberts, A. L., & Martin, L. T. (2009). Childhood IQ and adult mental disorders : A test of the cognitive reserve hypothesis. *American Journal of Psychiatry, 166*, 50-57. doi:10.1176/appi.ajp.2008.08030343

Koike, S., Barnett, J., Jones, P. B., & Richards, M. (2018). Cognitive profiles in childhood and adolescence differ between adult psychotic and affective symptoms: a prospective birth cohort study. *Psychological Medicine, 48*(1), 11-22. doi:10.1017/S0033291717000393

Kother, U., Lincoln, T. M., & Moritz, S. (2018). Emotion perception and overconfidence in errors under stress in psychosis. *Psychiatry Research, 270*, 981-991. doi:10.1016/j.psychres.2018.03.044

Kurtz, M. M., & Gerraty, R. T. (2009). A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology, 23*(5), 551-562. doi:10.1037/a0016277

Lavoie, M. A., Plana, I., Bedard Lacroix, J., Godmaire-Duhaime, F., Jackson, P. L., & Achim, A. M. (2013). Social cognition in first-degree relatives of people with schizophrenia: a meta-analysis. *Psychiatry Research, 209*(2), 129-135. doi:10.1016/j.psychres.2012.11.037

Lee, J., Altshuler, L., Glahn, D. C., Miklowitz, D. J., Ochsner, K., & Green, M. F. (2013). Social and nonsocial cognition in bipolar disorder and schizophrenia: relative levels of impairment. *American Journal of Psychiatry, 170*(3), 334-341. doi:10.1176/appi.ajp.2012.12040490

MacCabe, J. H., Wicks, S., Lofving, S., David, A. S., Berndtsson, A., Gustafsson, J. E., . . . Dalman, C. (2013). Decline in cognitive performance between ages 13 and 18 years and the risk for psychosis in adulthood: a Swedish longitudinal cohort study in males. *JAMA Psychiatry, 70*(3), 261-270. doi:10.1001/2013.jamapsychiatry.43

MacKenzie, L. E., Patterson, V. C., Zwicker, A., Drobinin, V., Fisher, H. L., Abidi, S., . . . Uher, R. (2017). Hot and cold executive functions in youth with psychotic symptoms. *Psychological Medicine, 47*(16), 1-10. doi:10.1017/S0033291717001374

MacKenzie, L. E., Uher, R., & Pavlova, B. (2019). Cognitive performance in first-degree relatives of individuals with vs without major depressive disorder: A meta-analysis. *JAMA Psychiatry, 76*, 297-305. doi:10.1001/jamapsychiatry.2018.3672

Mannie, Z. N., Williams, C., Browning, M., & Cowen, P. J. (2015). Decision making in young people at familial risk of depression. *Psychological Medicine, 45*, 375-380. doi:10.1017/S0033291714001482

Martinez-Aran, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sanchez-Moreno, J., . . . Salamero, M. (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *American Journal of Psychiatry, 161*, 262-270. doi:10.1176/appi.ajp.161.2.262

Maselko, J., Sikander, S., Bhalotra, S., Bangash, O., Ganga, N., Mukherjee, S., . . . Rahman, A. (2015). Effect of an early perinatal depression intervention on long-term child development outcomes: Follow-up of the thinking healthy programme randomised controlled trial. *The Lancet Psychiatry, 2*, 609-617. doi:10.1016/S2215-0366(15)00109-1

Maziade, M., Rouleau, N., Merette, C., Cellard, C., Battaglia, M., Marino, C., . . . Roy, M. A. (2011). Verbal and visual memory impairments among young offspring and healthy adult relatives of patients with schizophrenia and bipolar disorder: selective generational patterns indicate different developmental trajectories. *Schizophrenia Bulletin, 37*(6), 1218-1228. doi:10.1093/schbul/sbq026

McCarthy, J. B., Weiss, S. R., Segovich, K. T., & Barbot, B. (2016). Impact of psychotic symptoms on cognitive functioning in child and adolescent psychiatric inpatients with severe mood disorders. *Psychiatry Research, 244*, 223-228. doi:10.1016/j.psychres.2016.07.049

McGrath, J. J., Féron, F. P., Burne, T. H. J., Mackay-Sim, A., & Eyles, D. W. (2009). The neurodevelopmental hypothesis of schizophrenia: a review of recent

developments. *Annals of Medicine, 35*(2), 86-93. doi:10.1080/07853890310010005

Wisconsin Card Sorting Test 1571-1572 (Springer US 2011).

McIntyre, R. S., Cha, D. S., Soczynska, J. K., Woldeyohannes, H. O., Gallaugher, L. A., Kudlow, P., . . . Baskaran, A. (2013). Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depression and Anxiety, 30*, 515-527. doi:10.1002/da.22063

McTeague, L. M., Goodkind, M. S., & Etkin, A. (2016). Transdiagnostic impairment of cognitive control in mental illness. *Journal of Psychiatric Research, 83*, 37-46. doi:10.1016/j.jpsychires.2016.08.001

Meier, M. H., Caspi, A., Reichenberg, A., Keefe, R. S. E., Fisher, H. L., Harrington, H., . . . Moffi, T. E. (2014). Neuropsychological decline in schizophrenia from the premorbid to the postonset period: Evidence from a population-representative longitudinal study. *American Journal of Psychiatry, 171*, 91-101.

Mendez, I., Axelson, D., Castro-Fornieles, J., Hafeman, D., Goldstein, T. R., Goldstein, B. I., . . . Birmaher, B. (2019). Psychotic-like experiences in offspring of parents with bipolar disorder and community controls: A longitudinal study. *Journal of the American Academy of Child and Adolescent Psychiatry, 58*(5), 534-543 e536. doi:10.1016/j.jaac.2018.09.440

Miller, T. J., Mcglashan, T. H., Rosen, J. L., Cadenhead, K., Ventura, J., Mcfarlane, W., . . . Woods, S. W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity ,

interrater reliability , and training to reliability. *Schizophrenia Bulletin, 29*, 703-716.

Mollon, J., David, A. S., Morgan, C., Frissa, S., Glahn, D., Pilecka, I., . . . Reichenberg, A. (2016). Psychotic experiences and neuropsychological functioning in a population-based sample. *JAMA Psychiatry, 73*(2), 129-138. doi:10.1001/jamapsychiatry.2015.2551

Mollon, J., David, A. S., Zammit, S., Lewis, G., & Reichenberg, A. (2018). Course of Cognitive development from infancy to early adulthood in the psychosis spectrum. *JAMA Psychiatry, 75*(3), 270-279. doi:10.1001/jamapsychiatry.2017.4327

Moraros, J., Nwankwo, C., Patten, S. B., & Mousseau, D. D. (2017). The association of antidepressant drug usage with cognitive impairment or dementia, including alzheimer disease: A systematic review and meta-analysis. *Depression and Anxiety, 34*(3), 217-226. doi:10.1002/da.22584

Murphy, F. C., Rubinsztein, J. S., Michael, A., Rogers, R. D., Robbins, T. W., Paykel, E. S., & Sahakian, B. J. (2001). Decision-making cognition in mania and depression. *Psychological Medicine, 31*, 679-693.

Murray, R., & Lewis, S. (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal, 295*, 681-682.

Niarchou, M., Zammit, S., Walters, J., G, L., Owen, M. J., Owen, M. J., & van den Bree, M. B. (2013). Defective processing speed and nonclinical psychotic experiences in children: longitudinal analyses in a large birth cohort. *American Journal of Psychiatry, 170*, 550-557.

Nuechterlein, K. H., & Green, M. F. (2006). *MATRICS Consensus Cognitive Battery manual*. USA: MATRICS Assessment Inc.

Nuechterlein, K. H., Green, M. F., Kern, R., Baade, L., Barch, D. M., Cohen, J., . . . Marder, S. R. (2008). The MATRICS consensus cognitive battery, Part 1: Test selection, reliability, and validity. *American Journal of Psychiatry, 165*, 203-213.

Olfson, M., Lewis-Fernandez, R., Weissman M. M., Feder, A., Gameroff, M. J., Pilowsky, D., Fuentes, M. (2002). Psychotic symptoms in an urban general medicine practice. *American Journal of Psychiatry, 159*(8), 1412-1419.

Orellana, G., & Slachevsky, A. (2013). Executive functioning in schizophrenia. *Frontiers in Psychiatry, 4*, 35-128. doi:10.3389/fpsyt.2013.00035

Osler, M., Lawlor, D., & Nordentoft, M. (2007). Cognitive function in childhood and early adulthood and hospital admission for schizophrenia and bipolar disorders in Danish men born in 1953. *Schizophrenia Research, 92*, 132-141.

Paccalet, T., Gilbert, E., Berthelot, N., Marquet, P., Jomphe, V., Lussier, D., . . . Maziade, M. (2016). Liability indicators aggregate many years before transition to illness in offspring descending from kindreds affected by schizophrenia or bipolar disorder. *Schizophr Research, 175*(1-3), 186-192. doi:10.1016/j.schres.2016.04.038

Patel, K., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: Overview and treatment options. *Pharmacy and Therapeutics, 39*, 638-645.

Polanczyk, G., Moffitt, T. E., Arseneault, L., Cannon, M., Ambler, A., Keefe, R. S. E., . . . Caspi, A. (2010). Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Archives of General Psychiatry, 67*, 328-338. doi:10.1001/archgenpsychiatry.2010.14

Porritt, L. L., Zinser, M. C., Bachorowski, J-A., Kaplan, P. S. (2014). Depression diagnoses and fundamental frequency-based acoustic cues in maternal infant-directed speech. *Language Learning and Development*, 10: 51-67.

Poulton, R., Caspi, a., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Archives of General Psychiatry, 57*, 1053-1058. doi:10.1001/archpsyc.57.11.1053

Rabe-Hesketh, S. (2015). Generalized linear latent and mixed models.

Rapoport, J. L., Addington, A. M., Frangou, S., & Psych, M. R. (2005). The neurodevelopmental model of schizophrenia: update 2005. *Molecular Psychiatry, 10*(5), 434-449. doi:10.1038/sj.mp.4001642

Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: update 2012. *Molecular Psychiatry, 17*(12), 1228-1238. doi:10.1038/mp.2012.23

Rasic, D., Hajek, T., Alda, M., & Uher, R. (2014). Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. *Schizophrenia Bulletin, 40*, 28-38. doi:10.1093/schbul/sbt114

Reichenberg, A., Weiser, M., Rabinowitz, J., Caspi, A., Schmeidler, J., Mordechai, M., . . . Davidson, M. (2002). A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *American Journal of Psychiatry, 159*, 2027-2035.

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine, 44*, 2029-2040. doi:10.1017/S0033291713002535

Roddy, S., Tiedt, L., Kelleher, I., Clarke, M. C., Murphy, J., Rawdon, C., . . . Cannon, M. (2012). Facial emotion recognition in adolescents with psychotic-like experiences: a school-based sample from the general population. *Psychological Medicine, 42*(10), 2157-2166. doi:10.1017/S0033291712000311

Sahakian, B. J., Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *Journal of the Royal Society of Medicine, 85*, 399-402.

Santucci, A. K., Singer, L. T., Wisniewski, S. R., Luther, J. F., Eng, H. F., Dills, J. L., . . . Wisner, K. L. (2014). Impact of prenatal exposure to serotonin reuptake inhibitors or maternal major depressive disorder on infant developmental outcomes. *Journal of Clinical Psychiatry, 75*, 1088-1095. doi:10.4088/JCP.13m08902

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophrenia Research, 150*(1), 42-50. doi:10.1016/j.schres.2013.07.009

Schaefer, J. D., Scult, M. A., Caspi, A., Arseneault, L., Belsky, D. W., Hariri, A. R., . . . Moffitt, T. E. (2017). Is low cognitive functioning a predictor or consequence of major depressive disorder? A test in two longitudinal birth cohorts. *Development and Psychopathology*, 1-15. doi:10.1017/S095457941700164X

Schaefer, J. D., Scult, M. A., Caspi, A., Arseneault, L., Belsky, D. W., Hariri, A. R., . . . Moffitt, T. E. (2017). Is low cognitive functioning a predictor or consequence of

major depressive disorder? A test in two longitudinal birth cohorts. *Development and Psychopathology*. doi:10.1017/S095457941700164X

Schulz, J., Sundin, J., Leask, S., & Done, D. J. (2014). Risk of adult schizophrenia and its relationship to childhood IQ in the 1958 British birth cohort. *Schizophrenia Bulletin, 40*(1), 143-151. doi:10.1093/schbul/sbs157

Scott, J., Martin, G., Welham, J., Bor, W., Najman, J., O'Callaghan, M., . . . McGrath, J. (2009). Psychopathology during childhood and adolescence predicts delusional-like experiences in adults: a 21-year birth cohort study. *American Journal of Psychiatry, 166*, 567.

Scult, M. A., Paulli, A. R., Mazure, E. S., Moffitt, T. E., Hariri, A. R., & Strauman, T. J. (2017). The association between cognitive function and subsequent depression: a systematic review and meta-analysis. *Psychological Medicine, 47*(1), 1-17. doi:10.1017/S0033291716002075

Seidman, L. J., Cherkerzian, S., Goldstein, J. M., Agnew-Blais, J., Tsuang, M. T., & Buka, S. L. (2013). Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England Family Studies. *Psychological Medicine, 43*, 119-131. doi:10.1017/S0033291712000773

Seidman, L. J., Shapiro, D. I., Stone, W. S., Woodberry, K. A., Ronzio, A., Cornblatt, B. A., . . . Woods, S. W. (2016). Association of Neurocognition With Transition to Psychosis: Baseline Functioning in the Second Phase of the North American Prodrome Longitudinal Study. *JAMA Psychiatry, 73*(12), 1239-1248. doi:10.1001/jamapsychiatry.2016.2479

Shilyansky, C., Williams, L. M., Gyurak, A., Harris, A., Usherwood, T., & Etkin, A. (2016). Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. *The Lancet Psychiatry, 3*(5), 425-435. doi:10.1016/s2215-0366(16)00012-2

Simon, A. E., Grädel, M., Cattapan-Ludewig, K., Gruber, K., Ballinari, P., Roth, B., & Umbricht, D. (2012). Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. *Schizophrenia Research, 142*(1-3), 108-115. doi:10.1016/j.schres.2012.09.004

Simonsen, C., Sundet, K., Vaskinn, A., Birkenaes, A. B., Engh, J. A., Faerden, A., . . . Andreassen, O. A. (2011). Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. *Schizophrenia Bulletin, 37*(1), 73-83. doi:10.1093/schbul/sbp034

Singla, D. R., Kumbakumba, E., & Aboud, F. E. (2015). Effects of a parenting intervention to address both maternal psychological wellbeing and child development and growth in rural Uganda: a community-based, cluster randomised trial. *The Lancet Global health, 3*, e458-e469. doi:10.1016/S2214-109X(15)00099-6

Sitskoorn, M. M., Aleman, A., Ebisch, S. J. H., Appels, M. C. M., & Kahn, R. S. (2004). Cognitive deficits in relatives of patients with schizophrenia: A meta-analysis. *Schizophrenia Research, 71*, 285-295. doi:10.1016/j.schres.2004.03.007

Smith, M. J., Barch, D. M., & Csernansky, J. G. (2009). Bridging the gap between schizophrenia and psychotic mood disorders: Relating neurocognitive deficits to

psychopathology. *Schizophrenia Research, 107*(1), 69-75. doi:10.1016/j.schres.2008.07.014

Snitz, B. E., MacDonald, A. W., & Carter, C. S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophrenia Bulletin, 32*, 179-194. doi:10.1093/schbul/sbi048

Sullivan, P. F., Neale, M. C., Ph, D., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry, 157*, 1552-1562. doi:10.1176/appi.ajp.157.10.1552

Szoke, A., Schurhoff, F., Mathieu, F., Meary, A., Ionescu, S., & Leboyer, M. (2005). Tests of executive functions in first-degree relatives of schizophrenic patients: a meta-analysis. *Psychological Medicine, 35*, 771-782.

Trisha, C., Golnoush, A., Jan-Marie, K., Torres, I. J., & Yatham, L. N. (2018). Cognitive functioning in first episode bipolar I disorder patients with and without history of psychosis. *Journal of Affective Disorders, 227*, 109-116. doi:10.1016/j.jad.2017.10.003

U.S. Census Bureau. 2010 Resident Population. (2010).

Uher, R., Cumby, J., Mackenzie, L. E., Morash-conway, J., Glover, J. M., Aylott, A., . . . Alda, M. (2014). A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. *BMC Psychiatry*, 1-14. doi:10.1186/s12888-014-0344-2

Underwood, R., Peters, E., & Kumari, V. (2015). Psychobiology of threat appraisal in the context of psychotic experiences: A selective review. *European Psychiatry, 30*, 817-829. doi:10.1016/j.eurpsy.2015.07.001

Vatcheva, K. P., Lee, M., McCormick, J. B., & Rahbar, M. H. (2016). Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. *Epidemiology, 6*(2), 227-251. doi:10.4172/2161-1165.1000227

Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., . . . Murray, C. J. L. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet, 386*(9995), 743-800. doi:10.1016/s0140-6736(15)60692-4

Wang, Y. G., Shi, J. F., Roberts, D. L., Jiang, X. Y., Shen, Z. H., Wang, Y. Q., & Wang, K. (2015). Theory-of-mind use in remitted schizophrenia patients: The role of inhibition and perspective-switching. *Psychiatry Research, 229*(1-2), 332-339. doi:10.1016/j.psychres.2015.06.043

Wechsler, D. (1997). *Wechsler Memory Scale* (Third ed.). San Antonio, TX: Psychological Corporation.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence* (Second ed.). San Antonio, TX: Psychological Corporation.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children* (Fourth ed.). San Antonio, TX: Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale* (Fourth ed.). San Antonio, TX: Psychological Corporation.

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry, 44*, 660-669.

Whiffen, V. E., & Gotlib, I. H. (1989). Infants of postpartum depressed mothers: temperament and cognitive status. *Journal of Abnormal Psychology, 98*, 274-279. doi:10.1037/0021-843X.98.3.274

Wigman, J. T., de Vos, S., Wichers, M., van Os, J., & Bartels-Velthuis, A. A. (2017). A Transdiagnostic Network Approach to Psychosis. *Schizophrenia Bulletin, 43*(1), 122-132. doi:10.1093/schbul/sbw095

Wigman, J. T. W., Van Nierop, M., Vollebergh, W. A. M., Lieb, R., Beesdo-Baum, K., Wittchen, H. U., & Van Os, J. (2012). Evidence that psychotic symptoms are prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity - implications for diagnosis and ultra-high risk research. *Schizophrenia Bulletin, 38*, 247-257. doi:10.1093/schbul/sbr196

Winters, K. C., Stone, A. A., Weintraub, S., & Neale, J. M. (1981). Cognitive and attentional deficits in children vulnerable to psychopathology. *Journal of Abnormal Child Psychology, 9*, 435-453. doi:10.1007/BF00917794

Zammit, S., Allebeck, P., David, A. S., Dalman, C., Hemmingsson, T., Lundberg, I., & Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Archives of General Psychiatry, 61*, 354-360.

Zammit, S., Hamshere, M., Dwyer, S., Georgiva, L., Timpson, N., Moskvina, V., . . . O'Donovan, M. C. (2013). A population-based study of genetic variation and psychotic experiences in adolescents. *Schizophrenia Bulletin*, 1-9. doi:10.1093/schbul/sbt146

Zammit, S., Horwood, J., Thompson, A., Thomas, K., Menezes, P., Gunnell, D., . . . Harrison, G. (2008). Investigating if psychosis-like symptoms (PLIKS) are associated with family history of schizophrenia or paternal age in the ALSPAC birth cohort. *Schizophrenia Research, 104*(1-3), 279-286. doi:10.1016/j.schres.2008.04.036

Zammit, S., Kounali, D., Cannon, M., David, A. S., Gunnell, D., Heron, J., . . . Lewis, G. (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *American Journal of Psychiatry, 170*, 742-750. doi:10.1176/appi.ajp.2013.12060768

Zaninotto, L., Guglielmo, R., Calati, R., Ioime, L., Camardese, G., Janiri, L., . . . Serretti, A. (2015). Cognitive markers of psychotic unipolar depression: a meta-analytic study. *Journal of Affective Disorders, 174*, 580-588. doi:10.1016/j.jad.2014.11.027

Ziermans, T. B. (2013). Working memory capacity and psychotic-like experiences in a general population sample of adolescents and young adults. *Frontiers in Psychiatry, 4*, 161. doi:10.3389/fpsyt.2013.00161

APPENDIX A

COGNITIVE PROTOCOL

APPENDIX A – COGNITIVE PROTOCOLS

FORBOW Cognitive Scripts/Cover Sheets

Year 1 Cognitive Script & Cover Sheet

Before you begin, ensure that the necessary test materials are in order, and that the child is engaged in the testing process (refer to chapter 3 of WASI manual for guidelines for establishing and maintaining rapport). Reassure the child that it is all right to take breaks and that he or she should tell you when a break is needed. When you feel that you have attained a sufficient level of rapport and engagement, begin subtest administration.

Examinees will differ in the amount of explanation they require. Try to avoid the words ***intelligence*** or ***test*** because they may cause unnecessary anxiety. If the examinee expresses misconceptions about the testing, address these concerns in a truthful, nonthreatening manner.

Age specific protocol	Measure in order of administration	Version by age	Instructions' Location
	* Assent/consent		
	1. Age 3+: Gen IQ	6+: WASI	User Manual
	2. Age 6+: Letter number	6-15: WISC 16+: WAIS	User manual OR separate script
	3. Age 6+: Coding	6-7 WPPSI 8-15: WISC 16+: WAIS	User manual OR separate script
	4. Age 6+: CVLT-C		Record form
	5. Age 8+: Verbal Fluency	8-13: D-KEFS ***Alternate***	DKEFS - Manual in easel position
	6. Age 5+: Stories Immediate	5-8: CMS A&B 9-12: CMS C&D 13-15: CMS E&F 16+: WMS-IV	Separate script
	* Stories 25 minute delay: complete saliva collection, measurements, questionnaires		
	7. Age 5+ Stories Recall	*	*
	8. Age 8+: CANTAB CGT		User Manual (ascending first shortened)
	9. Age 7+: CANTAB SWM		User Manual (sh-3x3p-2X4-40-2X6-60-2X8-80-2X10-120)

Notes on confidence/doubt in validity of assessment:

Notes (other):

Double scored on _____ by _____