VISUAL MEMORY AND PSYCHOTIC SYMPTOMS IN OFFSPRING OF PARENTS WITH SEVERE MENTAL ILLNESS

by

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ABSTRACT

Severe mental illness refers to functionally impairing disorders such as major depressive disorder, bipolar disorder, and schizophrenia. Available treatments for severe mental illness have limited efficacy. Thus, there is a need to identify youth at risk and provide pre-emptive interventions before illness onset. I sought to examine visual memory and risk of mental illness in youth. First, I explored the relationship between visual memory and family history of mental illness. I found that offspring of parents with mental illness had lower visual memory performance compared to offspring of parents without mental illness. Second, I explored the relationship between visual memory and psychotic symptoms, an early manifestation of risk of mental illness. I found that lower visual memory performance among youth was associated with increased likelihood of experiencing psychotic symptoms. These findings clarify the relationship between risk of mental illness and visual memory and may inform future targeted early interventions.

LIST OF ABBREVIATIONS USED

ADHD	Attention-Deficit/ Hyperactivity Disorder
ASD	Autism Spectrum Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
FORBOW	Families Overcoming Risks and Building Opportunities for Well-Being
FSIQ	Full-Scale Intelligence Quotient
IQ	Intelligence Quotient
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
NSMI	Non-Severe Mental Illness
OR	Odds Ratio
RCFT	Rey Complex Figure Test
SCID-5	Structured Clinical Interview for DSM-5
SIPS	Structured Interview for Prodromal Syndromes
SMI	Severe Mental Illness
WASI-II	Wechsler Abbreviated Scale of Intelligence – Second Edition

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CHAPTER 1 GENERAL INTRODUCTION

1.1 Severe Mental Illness

Severe Mental Illness (SMI) refers to a transdiagnostic category of disorders including major depressive disorder, bipolar disorder, and schizophrenia[1]. SMI are impairing and frequently chronic disorders that start early in life and cause great burden to the individual as well as society[2]. Treatments are available to reduce the symptoms of SMI. However, these treatments rarely are successful at returning individuals to their prior level of functioning before they were diagnosed[3,4].

1.2 Cognitive functioning in SMI

Individuals with SMI generally perform poorer on cognitive tests[5,6]. Lower cognitive performance among individuals with SMI has been demonstrated within wide cognitive domains including executive functioning,[7]and verbal and visual memory[8,9]. Cognition among individuals with SMI has typically been examined in a diagnosis specific approach.

Schizophrenia is typically associated with lower cognitive performance in comparison to controls. This has been well-established in previous literature with moderate to large effect sizes demonstrating lower performance compared to controls across a large range cognitive domains including general intelligence, executive functioning, attention, memory, motor performance, spatial ability, and language.[10] Lower cognitive performance compared to controls has also been observed in bipolar disorder, both bipolar 1 and bipolar 2[9,11]. While lower cognitive performance is present in bipolar 1 and 2 compared to controls, the effect sizes are frequently smaller in bipolar 2 compared to bipolar 1 in cognitive domains such as memory, executive functioning, and attention[11]. Notably, individuals with schizophrenia and bipolar disorder have lower cognitive scores that are frequently maintained longitudinally[5]. A recent meta-analysis by Bora and Ozerdem

examined longitudinal studies of cognition in bipolar disorder in comparison to individuals with schizophrenia and controls. This meta-analysis included studies with individuals with bipolar disorder who were euthymic, mildly symptomatic, and definitively symptomatic. Bora and Ozerdem found that lower cognitive performance across many domains, including global cognition, processing speed, executive functioning, and sustained attention, is typically stable in bipolar disorder after onset, similar to that of schizophrenia[5]. Individuals with major depressive disorder demonstrate lower cognitive performance while ill in cognitive domains including executive functioning, memory, and attention[12]. This decreased cognitive performance remains when individuals with major depressive disorder are euthymic, though this is typically a smaller difference in performance compared to controls than when individuals are ill[6,12] .

For this work, my focus of interest is the less researched area of visual memory. Individuals with first-episode psychosis[13], schizophrenia[8], bipolar disorder[9], and depression[14] perform lower on tests of visual memory. Furthermore, unaffected relatives of individuals with SMI have demonstrated decreased cognitive performance on tests of visual memory[15]. It is possible that cognitive performance may be a risk marker for SMI that can be useful to investigate the pathology of illness as well as predict who is most at risk of developing SMI in the future.

1.3 Prevention of SMI

Once an individual develops SMI, even with available treatments, they rarely return to their prior level of functioning before they developed illness[3,4]. Thus, pre-emptive inventions earlier on in the life span before the onset of SMI may be necessary[16]. Two broad forms of intervention strategies have been described in the literature: (1) universal prevention and (2) targeted prevention. Targeted prevention can be further divided into selective and indicated prevention. Universal prevention includes all individuals in a population, selective prevention includes

individuals who are at increased risk of a disorder, and indicated prevention includes individuals who are experiencing early symptoms[17]. It has been reported that the effects of targeted interventions are superior to those of universal interventions, specifically investigated in the context of internalizing disorders[18]. A Cochrane review examining the efficacy of universal and targeted prevention strategies for depression found that targeted prevention studies had consistently larger effects than universal prevention studies[19]. In order to design targeted interventions, it is important to identify which children and youth are most at risk of developing SMI.

1.4 Prediction of SMI

Offspring of parents with SMI are 2.5 times more likely to develop SMI themselves by early adulthood. Familial risk is not specific to parent diagnosis[20]. For example, a child of a parent with major depressive disorder has an increased risk of bipolar disorder compared to a child without parental history of SMI. Thus, it is necessary to use a transdiagnostic approach to identify risk for SMI[1]. However, most people in the general population who develop a SMI do not have a known family history of SMI[21]. Thus, it is necessary to establish different risk factors to identify vulnerable youth in addition to a family history of SMI.

1.5 Early manifestations of risk for SMI

There are early manifestations of risk for SMI that are present in childhood and adolescence that precede and predict future onset of SMI. Examples of early manifestations of risk include anxiety, psychotic symptoms, and poorer cognitive development[22]. The current work focuses on two early manifestations of SMI: cognitive ability and psychotic symptoms. Changes in cognitive functioning have been shown to be predictive of later psychotic illness[23]. Psychotic symptoms refer to hallucinations and delusions that are transient and occur in individuals who do

not meet criteria for a psychotic disorder[24]. Psychotic symptoms are common during childhood and adolescence and are associated with risk of future mental illness [25,26].

1.6 Neurodevelopmental hypothesis

The neurodevelopmental theory of schizophrenia refers to the idea that changes to the brain early on in development influence the development of schizophrenia later in life. This model has been recently reintroduced as the Developmental Risk Factor Model which posits that the development of psychosis involves interactions of multiple genetic and environmental factors similar to other chronic illnesses like heart disease[27]. According to this model, the development of psychosis may be associated with developmental cognitive impairment as well as other established risk factors such as familial risk or urbanicity[28]. The Development Risk Factor Model moves towards thinking of psychosis as a spectrum with schizophrenia reflecting the severe end of this spectrum[29]. The Dunedin Longitudinal Study found that children who later developed schizophrenia exhibited deficits in knowledge acquisition, reasoning, processing speed, visuospatial problem solving, and working memory in comparison to peers[23]. For children who later developed schizophrenia, these deficits gradually increased throughout childhood and adolescence. Another result from the Dunedin Longitudinal Study found that the same individuals who later developed psychotic illness were more likely to report psychotic symptoms during childhood in comparison to peers[25].

1.7 Cognitive functioning among individuals at familial risk of SMI

The majority of current literature has explored cognitive functioning of individuals at risk of mental illness using a disorder specific lens. A recent meta-analysis comparing cognition in first-degree relatives of individuals with major depressive disorder to controls found that lower general cognitive performance is associated with familial risk of major depressive disorder[30]. This

meta-analysis examined a wide range of cognitive domains and found domain specific decreased cognitive performance in first-degree relatives of individuals with major depressive disorder in the domains of Full-Scale IQ, memory, verbal intelligence, perceptual intelligence, language, and academic performance. Among offspring of parents with schizophrenia and bipolar disorder, lower cognitive performance compared to controls has been demonstrated in many cognitive domains including executive functioning, verbal memory, and visual memory[15,31]. A large multi-site study by Hemager and colleagues extensively explored cognition among offspring of parents with schizophrenia and bipolar disorder in comparison to controls at age 7[32]. Among these young offspring, this study found that offspring of parents with schizophrenia demonstrated significantly poorer cognitive performance on a broad range of cognitive domains including processing speed, working memory, executive functioning, and visual memory. However, this study found only small decreases in cognitive performance among offspring of parents with bipolar disorder and controls. The current literature could benefit from research on cognitive functioning transdiagnostically among offspring of parents with SMI at a variety of ages. The literature would also benefit from thorough investigations into less researched cognitive domains among offspring of parents with SMI such as visual memory. A current gap in the literature is a lack of exploration of the impact of severity of parental mental illness on offspring cognition in less researched domains such as visual memory.

1.8 Visual memory performance as an indicator of risk

Poorer memory performance, both visual and verbal, has been demonstrated among offspring of parents with schizophrenia and bipolar disorder[15]. Visual memory refers to the encoding, storage, and retrieval of visual stimuli and is one aspect of the larger concept of non-verbal cognition[33]. In a recent study, Maziade and colleagues[34] explored both visual memory and

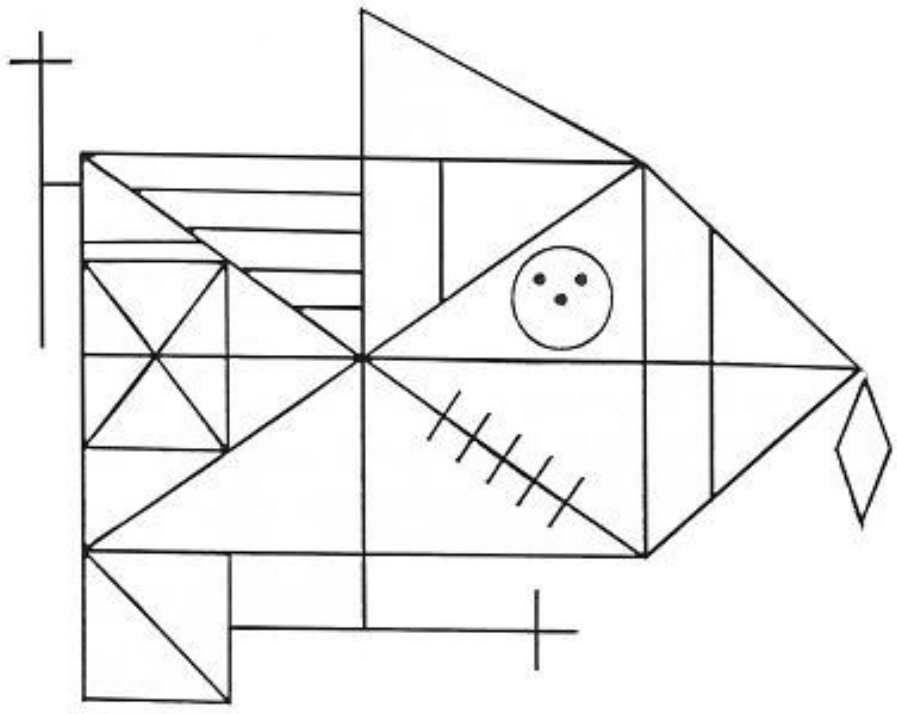
verbal memory in youth and adults to better understand the trajectories of memory impairments among individuals at familial risk for schizophrenia and bipolar disorder. This work compared visual memory and verbal memory among youth at familial risk of schizophrenia and bipolar disorder, nonaffected adult relatives, adults with schizophrenia or bipolar disorder, and controls. The comparison of memory performance in at-risk youth to adults who did or did not develop illness allowed Maziade and colleagues to explore the trajectory of both visual and verbal memory performance. Maziade and colleagues found that verbal memory was similarly poor in at-risk youth, non-affected adults with familial history of schizophrenia or bipolar disorder, and adults with schizophrenia or bipolar disorder in comparison to controls. In contrast, while their analysis of visual memory demonstrated that visual memory was similarly poor in at-risk youth and adults with schizophrenia or bipolar disorder, non-affected adult relatives performed more similarly to controls. This was not observed in verbal memory, only visual memory. This suggests that visual memory performance may be more promising than verbal memory in predicting which offspring at familial risk for schizophrenia or bipolar disorder are most at risk of developing illness in the future. Based on this, visual memory could benefit from further investigation in a population of relatives of individuals with a broad range of SMI.

1.9 Visual memory and the Rey Complex Figure Test

The Rey Complex Figure Test (RCFT) is a widely used neuropsychological tool designed to measure executive functioning, constructional ability, and visual constructional memory[35,36]. The RCFT asks individuals to copy an intricate figure (Figure 1) that is not easily recognizable onto a separate piece of paper. Individuals are then asked to draw the figure again from memory twice. In the immediate recall condition, individuals are asked to recall the figure 3 minutes after last seeing it and in the delayed recall condition individuals are asked to recall the figure 30 minutes

after last seeing it. After the recall conditions, individuals complete a recognition trial in which they are shown 24 images and are asked to recall which images were part of the original figure they copied. We elected to use the delayed recall accuracy score of the RCFT as our measure of visual memory based on its demonstrated ability to detect visual memory performance differences between individuals with SMI and controls[9] and between offspring of individuals with mental illness and controls[15]. The RCFT is the same measure that Maziade and colleagues used to assess visual memory and found as a potential predictor of developing schizophrenia or bipolar disorder in adulthood[34].

Figure 1. Rey Complex Figure Test stimulus[35]



1.10 Aims

We investigated the relationship between visual memory and risk of mental illness in two ways. First, we explored the relationship between visual memory and family history in a sample

of youth with and without familial risk of mental illness. We explored family history using severity groups of parental mental illness to investigate if offspring visual memory performance was associated with parental severity of illness. Then, we explored the relationship between visual memory and psychotic symptoms, an early manifestation of risk of mental illness.

CHAPTER 2
VISUAL MEMORY IN OFFSPRING OF PARENTS WITH MENTAL ILLNESS

Contribution Statement

I completed the data analysis and drafted the manuscript in this chapter under the supervision of Dr. Rudolf Uher. Data were collected by the FORBOW assessment team. I am an assessor on the FORBOW team and help collect clinical and cognitive data. I scored the RCFT for all participants.

2.1 Abstract

Background: Severe mental illness (SMI) refers to impairing and frequently chronic disorders that are difficult to treat. Lower cognitive performance early in life may be a manifestation of risk for SMI. Visual memory has been highlighted as a potential cognitive predictor of future risk of developing bipolar disorder and schizophrenia.

Methods: We examined visual memory in 214 participants ages 6-27 using the Rey Complex Figure Test (RCFT). Our sample included 37 offspring with no parental history of mental illness, 103 offspring with parental history of non-severe mental illness (NSMI), and 74 offspring with parental history of SMI. We tested the effects of family history of mental illness on visual memory using mixed-effects linear regression.

Results: After accounting for age, sex, and family clustering, we found that as severity of parental mental illness increases, offspring visual memory performance decreases significantly (b = -3.58, 95% CI -6.79 to -0.37, p = 0.029).

Conclusion: We found that severity of parental mental illness predicts visual memory ability. This finding may help identify youth most at risk of developing mental illness and thus inform future interventions.

2.2 Introduction

Individuals with severe mental illness (SMI) including major depressive disorder, bipolar disorder, and schizophrenia frequently experience chronic symptoms that are difficult to treat[1]. SMI is associated with lower cognitive performance across a wide range of domains[5,6,37]. Unaffected relatives of individuals with SMI exhibit lower performance across a range of cognitive domains including executive functioning, verbal memory, and visual memory[15,30,31]. Lower cognitive ability, particularly lower visual memory performance, may represent an early manifestation of increased risk for SMI among individuals with a known family history.

Lower visual memory performance has been observed among individuals at varying stages of mental illness progression[13] and also among unaffected relatives of individuals with SMI[15]. Visual memory performance has been suggested as a potential predictor of developing mental illness[34]. A recent study found that offspring of parents with bipolar disorder or schizophrenia, and adults diagnosed with bipolar disorder or schizophrenia performed worse than controls on a visual memory task. Young offspring of parents with bipolar disorder or schizophrenia and adults diagnosed with bipolar disorder or schizophrenia performed poorer than non-affected adult relatives. Visual memory differentiated offspring of parents with SMI from controls better than verbal memory[34]. This pattern of results suggests that visual memory may represent a powerful predictor of future risk of mental illness. It is known that unaffected relatives of individuals with depression have lower cognitive scores[30]. However, visual memory performance has yet to be examined among offspring of parents with a transdiagnostic range of mental illness including depression.

In the present study, we explored the relationship between parental psychopathology and offspring visual memory performance. It is currently unknown how severity of parental

psychopathology impacts offspring visual memory. We examined visual memory among offspring of parents with no lifetime history of any mental disorder, offspring of parents with non-severe mental illness (NSMI) and offspring of parents with SMI. For comparison with previous studies, we also report the relationship between parent diagnoses of schizophrenia, bipolar disorder, and major depressive disorder and offspring visual memory performance. We hypothesized that offspring visual memory performance would be lower among offspring of parents with more severe forms of mental illness.

2.3 Methods

2.3.1 Participants

We examined visual memory in 214 participants (109 females and 105 males) from the Families Overcoming Risks and Building Opportunities for Well-being (FORBOW) cohort. FORBOW is enriched for offspring of parents with SMI[22].We included 6-27 year old participants who completed the Rey Complex Figure Test (RCFT). We excluded participants with any known major genetic anomalies (e.g. 22q11 deletion syndrome), neurological illness (e.g. epilepsy), or intellectual disability of a degree incompatible with completing the assessments. Participants with capacity to make an informed decision provided written informed consent. For participants who could not provide informed consent, participants provided assent and a parent or guardian provided written informed consent.

2.3.2 Visual memory

Visual memory involves perceptual processing of a stimulus, encoding the stimulus into memory, and retrieving and recalling the memory[33].Visual memory was measured using the RCFT. The RCFT requires participants to copy a complex figure onto a separate piece of paper and then draw the figure again from memory. In the present study, participants were asked to draw the figure from memory 3 minutes (immediate recall) and then again 30 minutes (delayed recall) after last seeing it. After participants completed the delayed recall, they were asked to complete a recognition recall trial where they looked at 24 images and identified which were part of the original figure they copied. To ensure consistency across scoring, a single rater (EHV) who was blind to parent psychopathology scored all of the RCFTs. We used the quantitative scoring system[35] to score the RCFT. This method has been shown to have a median inter-rater reliability coefficient of 0.94[36]. Normative scores are available for ages 6-89[35]. Visual memory scores were

calculated by comparing the standard score of delayed recall condition accuracy among participants.

2.3.3 Parental psychopathology

Parent diagnosis was determined through the Structured Clinical Interview for DSM-5 (SCID-5)[38]. Parental SMI was defined as having a biological parent with a diagnosis of major depressive disorder, bipolar disorder, schizophrenia, schizoaffective disorder, or schizophreniform disorder that meets at least two of the five severity criteria. The severity criteria are past hospital admission, psychotic symptoms, suicide attempt, recurrence, and chronicity. Parent NSMI included mood disorders that did not meet severity criteria, obsessive compulsive disorder, post-traumatic stress disorder, anxiety disorders, and substance abuse. We defined NSMI and included this group to allow our analysis to test the impact of severity of parental mental illness. Controls were parents who did not meet criteria for a lifetime psychiatric disorder.

2.3.4 Offspring psychopathology

We assessed offspring for psychiatric disorders using semi-structured interviews with the offspring and their parents. For offspring ages 6-18, we used the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)[39] and for offspring age 18+, we used the Structured Clinical Interview for DSM-5 (SCID-5)[38]. Youth assessors were separate from parent assessors and were blind to parent psychopathology. We confirmed offspring diagnoses in consensus meetings with a psychiatrist or psychologist who was blind to parent psychopathology.

2.3.5 General cognitive ability

We measured offspring general cognitive ability using the full-scale intelligence quotient (FSIQ) of the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)[40]. The WASI-II FSIQ combines scores from four subtests: block design, vocabulary, matrix reasoning,

and similarities. The WASI-II was administered and double-scored by assessors trained in administration and scoring.

2.3.6 Statistical analyses

We examined the relationship between family history and visual memory using mixed-effects linear regression with familial risk of mental illness (0 = controls, 1 = parental NSMI, and 2 = parental SMI) as the independent variable and RCFT delayed recall standard scores as the dependent variable. We coded familial risk for mental illness as 0 = controls if the participant did not have a known biological parent with a psychiatric disorder. We coded this variable as 1 = parental NSMI if one or both biological parents had a psychiatric disorder that did not meet criteria for SMI defined above. This variable was coded as 2 = parental SMI if the participant had one or both biological parents with a diagnosis of a major mood or psychotic disorder that met two or more of the severity criteria defined above. We compared the effect of parent diagnosis on visual memory performance using mixed-effects linear regression that compared RCFT delayed recall standard scores of offspring of parents with depression, bipolar disorder, and schizophrenia to controls. We treated sex and age as fixed effect covariates. To address clustering within families, we used family identification as a random effect. We conducted sensitivity analyses to ensure that our results were not unduly affected by general cognitive ability (IQ) or the presence of neurodevelopmental disorders (attention-deficit/ hyperactivity disorder (ADHD) or autism spectrum disorder (ASD)). We report the beta values, their 95% confidence intervals, and p-values. We interpreted p-values below 0.05 as statistically significant. We completed our analysis using STATA 15.1 software.

2.4 Results

2.4.1 Demographic and clinical characteristics

Of the participants, 17.29% have both biological parents with no diagnosis, 48.13% have one or both biological parents with NSMI, and 34.58% have one or both biological parents with SMI. Table 2.1 presents the demographic and clinical characteristics for the sample.

Table 2.1 Demographic and clinical characteristics of offspring of control parents, parents with NSMI, and parents with SMI. * denotes statistically significant differences between groups. We tested differences between groups using X^2 (for categorical variables) and univariate ANOVAs (for continuous variables).

	No parent diagnosis	Parent NSMI	Parent SMI
Offspring n	37	103	74
Age, mean (SD)	12.80 (3.81)	11.97 (4.07)	13.58 (5.05)
n females (%)	17 (45.95)	46 (44.66)	46 (62.16)
IQ, mean (SD)	109.55 (12.16)	106.10 (12.38)	103.40 (13.40)
Offspring diagnosis, n (%)			
ADHD*	1 (2.70)	27 (26.21)	13 (17.57)
ASD	1 (2.70)	5 (4.85)	4 (5.41)

2.4.2 The relationship between parental mental illness and offspring visual memory

We explored the relationship between visual memory and parental mental illness in offspring of parents with no diagnosis, offspring of parents with NSMI, and offspring of parents with SMI. After accounting for age and sex as fixed-effect covariates, we found that as family history increased in severity from controls to SMI, visual memory performance decreased significantly (b = -3.58, 95% CI -6.79 to -0.37, p = 0.029; Table 2.2). This showed that as severity of parental

mental illness increased, offspring visual memory performance decreased. Figure 2 shows the means and standard error of RCFT delayed recall scores in offspring of parents with no diagnosis, NSMI, and SMI.

Figure 2. The mean RCFT delayed recall standard scores for offspring of control parents, parents with NSMI, and parents with SMI. Error bars represent standard error of the mean.

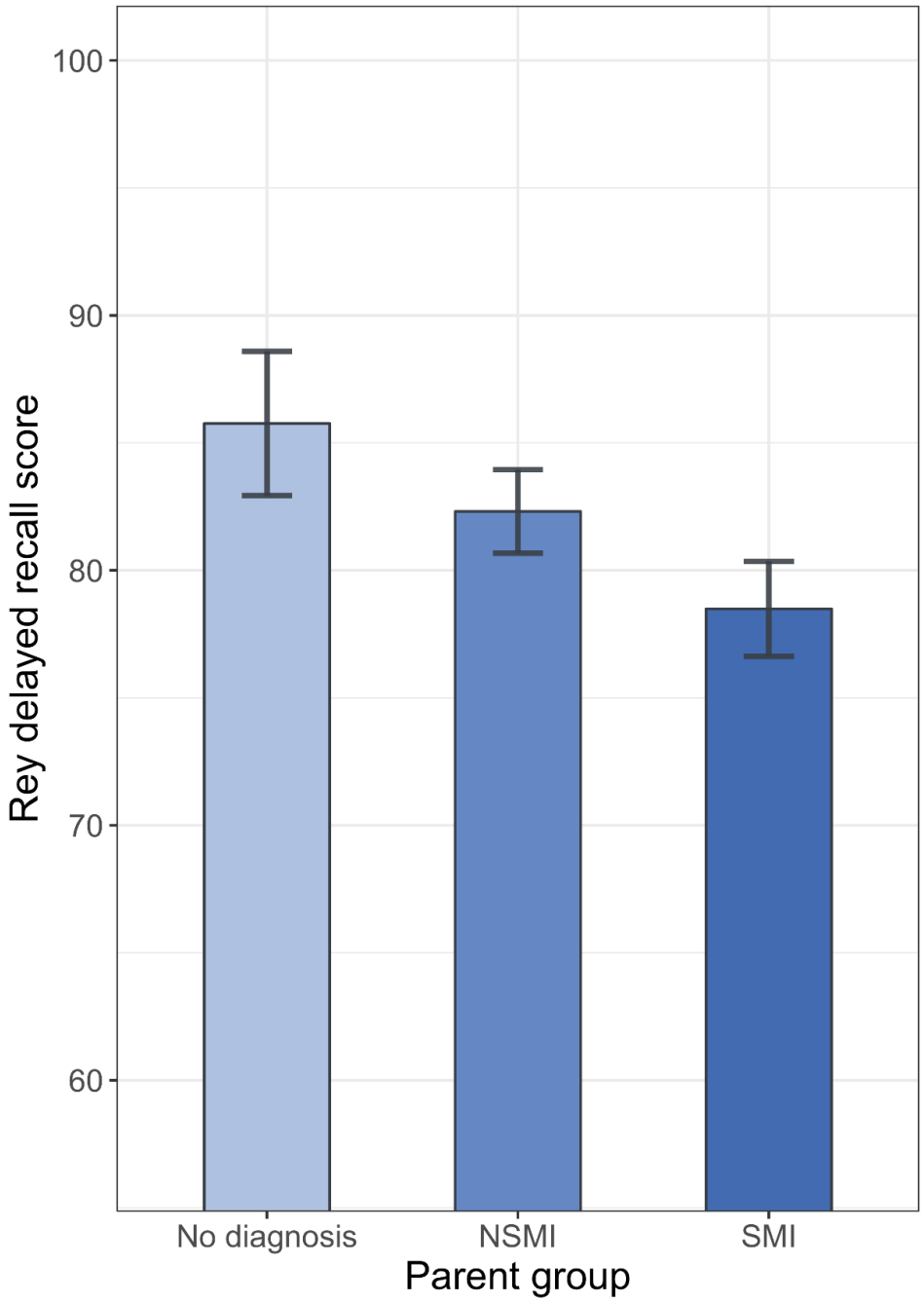


Table 2.2 Effect of family history of mental illness on visual memory using mixed-effects linear regression.

	b value	95% confidence interval lower	upper	p-value
Family history group	**-3.58**	**-6.79**	**-0.37**	**0.029**
Age (years)	-0.55	-1.05	-0.05	0.030
Sex (female)	3.29	-1.10	7.70	0.142

2.4.3 Effect of parent diagnosis on visual memory performance

To explore the specificity of the main results, we compared offspring of parents with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorder individually to controls. After accounting for age, sex, and family clustering, we found that visual memory performance was lower in offspring of parents with schizophrenia spectrum disorder in comparison to offspring of parents with no diagnosis (b = -11.16, 95% CI -20.23 to -2.08, p = 0.016; Table 1 in appendix). Although visual memory performance was also numerically lower among offspring of parents with major depressive disorder and bipolar disorder compared to control offspring, these differences were not statistically significant (please refer to Table 1 in appendix).

2.4.4 Sensitivity analyses

We performed sensitivity analyses to explore whether our finding may have been affected by general cognitive ability (IQ), diagnosis of ADHD, diagnosis of ASD, and RCFT recognition standard score. In all sensitivity analyses, our result was within one standard error of the original result (please refer to Tables 2-5 in the appendix).

2.5 Discussion

The present study replicates a previous finding that visual memory is a marker of familial risk for mental illness and extends it to a transdiagnostic range of non-severe and severe mental illness. We found that both offspring of parents with NSMI and SMI exhibit lower visual memory performance in comparison to controls. This relationship reflected lower visual memory performance as parental mental illness severity increased. Our results are consistent with previous findings of lower visual memory ability among offspring of parents with bipolar disorder and schizophrenia[15,31,34]. We expanded on current literature by examining visual memory performance in offspring of parents with mental illness transdiagnostically and including severity of parental psychopathology in analyses. We found that visual memory performance in offspring is related to the severity of parent psychopathology and that lower visual memory performance is exhibited transdiagnostically.

To allow comparison with previous studies, we explored how parent diagnosis may impact offspring visual memory performance. A recent large study of 7 year-old children at familial risk of schizophrenia and bipolar disorder found a difference in visual memory between controls and offspring of parents with schizophrenia, but not offspring of parents with bipolar disorder[32]. We found a similar relationship between offspring of parents with schizophrenia and controls. We also found a non-statistically significant difference between offspring of parents with bipolar disorder and controls; however, our effect was larger than this previous study[32]. Our findings included participants from a large age range with a higher mean age than this previous study and due to this we used standardized scores for our analysis and controlled for age in all analyses. It is possible that our older mean age and the use of standardized scores contributed to the slight differences between our findings and this previous study.

Future research should consider using the RCFT to measure visual memory based on its demonstrated ability to detect differences in visual memory performance between youth with and without family history of mental illness. The literature would benefit from longitudinal studies of visual memory performance during childhood and adolescence and its relationship with future onsets of mental illness by adulthood. Clinically, visual memory may need to be targeted in early interventions to prevent the onset of mental illness. Potential early interventions could use visual memory performance as one of the cognitive risk factors for allocation. While there are currently few interventions targeting cognitive performance in offspring of parents with mental illness, cognitive enhancement therapy is a promising intervention for social cognition among individuals with early psychosis[41]. Future long-term research to design and test interventions to improve cognitive development of offspring of parents with mental illness is necessary.

The present study benefits from a large well-characterized sample of offspring of parents with and without mental illness. We completed thorough assessments of parental psychopathology and psychopathology and cognition in offspring. This allowed us to run sensitivity analyses to test the impact of general cognitive ability as well as neurodevelopmental disorders within our cohort. We benefit from the inclusion of offspring of parents with no psychiatric disorders, non-severe mental illness, and severe mental illness allowing us to make novel comparisons between these groups. We also benefit from the inclusion of offspring of parents with major depressive disorder, bipolar disorder, and schizophrenia. We interviewed all participating parents within FORBOW for psychopathology before allocating them to the parental family history groups. The RCFT was scored by one author (EHV). This allows for consistency of scoring of the RCFT throughout our sample.

Our results should be interpreted in the context of several limitations. Our comparison of parental diagnosis of depression, bipolar disorder, or schizophrenia is limited in power by a relatively lower number of parents with schizophrenia within the FORBOW cohort. The relative lower number of enrollment may be reflective of the evidence that individuals with schizophrenia typically have fewer children[42]. Due to this, our comparison of visual memory performance based on parent diagnosis should be interpreted as preliminary. It is important to note that a limitation of using the RCFT is that due to practice effects it cannot be administered multiple times in a row. Thus, if we decided to explore repeated testing of visual memory with the RCFT[35] we would need to wait many years. The Modified Taylor Complex Figure was designed to assess similar domains for repeat testing of the RCFT and may perform similarly[43]. Future studies may explore repeated measures of visual memory using different complex figures in children and adolescents.

2.6 Conclusion

In conclusion, we found that offspring of parents with mental illness exhibit lower visual memory ability relative to offspring of parents with no psychiatric disorders. There was a relationship between severity of parent mental illness and offspring visual memory, with offspring of parents with severe mental illness performing poorer than offspring of parents with non-severe mental illness. Future studies may explore visual memory longitudinally in offspring of parents with mental illness and visual memory may be used to inform early interventions to prevent mental illness.

CHAPTER 3
VISUAL MEMORY AND PSYCHOTIC SYMPTOMS IN YOUTH

Contribution Statement

I completed the data analysis and drafted the manuscript in this chapter under the supervision of Dr. Rudolf Uher. Data were collected by the FORBOW assessment team. I am an assessor on the FORBOW team and help collect clinical and cognitive data. I scored the RCFT for all participants.

3.1 Abstract

Background: Psychotic symptoms are common during childhood and adolescence and may indicate transdiagnostic risk of future psychiatric disorders. Lower visual memory ability has been suggested as a potential indicator of future risk of mental illness. The relationship between visual memory and psychotic symptoms in youth has not yet been explored.

Methods: We examined visual memory and psychotic symptoms among 205 participants aged 7-27 years. We assessed visual memory using the Rey Complex Figure Test (RCFT) and psychotic symptoms using validated semi-structured interview measures. We tested the relationship between visual memory and psychotic symptoms using mixed-effects logistic regression.

Results: After accounting for age, sex, and family clustering, we found that psychotic symptoms were significantly associated with lower visual memory (OR = 1.80, 95% CI 1.06 to 3.06, p = 0.03). This result was unchanged after accounting for general cognitive ability.

Conclusion: Lower visual memory performance is associated with psychotic symptoms among youth, regardless of general cognitive ability. This finding may inform future targeted early interventions.

3.2 Introduction

Psychotic symptoms, including hallucinations and delusions, are the hallmark of schizophrenia and other psychotic disorders. Transient psychotic symptoms are common in the general population with estimates of 17% among children and 7.5% among adolescents in the absence of any psychotic disorder[24]. Psychotic symptoms in childhood and adolescence predict increased risk of psychotic disorders in adulthood[44]. Psychotic symptoms during childhood are an established risk factor for future psychopathology[26,44], with more persistent symptoms being more predictive than transitory ones[45,46]. However, not all youth with psychotic symptoms will develop mental illness by adulthood. Thus, it may be beneficial to identify additional risk markers that can improve the ability to predict which youth are at increased risk of major mood and psychotic disorders.

Lower cognitive performance has been demonstrated among individuals with psychotic disorders across many domains of cognition including executive functioning, processing speed, and both verbal and visual memory[20]. Individuals in both the early stages of psychosis and with long-standing psychotic illness have demonstrated lower visual memory ability in comparison to controls[13]. Among youth with a family history of psychotic disorders, lower cognitive ability has been associated with increased risk of illness[47]. Specifically, lower visual memory performance has been associated with risk of schizophrenia and bipolar disorder among youth with a family history of these disorders[34]. It is important to identify and characterize the cognitive profile of individuals at high risk of SMI to allow for the development of appropriate pre-emptive early interventions[16]. Poorer visual memory performance may indicate elevated risk for mental illness, especially among youth at familial high risk who are experiencing psychotic symptoms. Visual memory has been explored in youth with family history of mental illness[15,34] (see Chapter 2),

suggesting that visual memory may be an early manifestation of familial risk for mental illness. However, it is unknown if visual memory is poorer in children and adolescents who experience psychotic symptoms without meeting criteria for a psychotic disorder.

The link between psychotic symptoms and cognitive performance in youth has been examined, but there have been some inconsistencies across studies. It has been shown that lower general cognitive ability and theory of mind, but not executive functioning, at age 5 is associated with psychotic symptoms at age 12[48]. In contrast, another study found that youth with questionnaire measured psychotic-like experiences exhibit slightly lower general cognitive ability, memory, and executive functioning in comparison to youth without psychotic-like experiences[49]. Additionally, we have recently shown that 'hot' executive functions, involving emotion and motivation, are poorer among youth with psychotic symptoms but that there is no difference in performance on tasks assessing 'cold' executive functions, which do not involve emotion[50]. Conversely, lower processing speed at age 8 and lower attention at age 11 were weakly associated with psychotic symptoms at age 12 in a large birth cohort of children and youth. This study did not find differences in working memory or reasoning and problem solving between youth with and without psychotic symptoms[51]. While the literature on cognition in youth with psychotic symptoms is growing, there is not yet a consensus. It is important to study cognition of youth with psychotic symptoms particularly visual memory to better understand the neurocognitive mechanisms underlying psychotic symptoms and to inform potential early interventions.

In the present study, we aimed to explore the relationship between visual memory performance and psychotic symptoms. We assessed visual memory using the Rey Complex Figure Test (RCFT) and we assessed psychotic symptoms using validated semi-structured interviews in a cohort enriched for offspring of parents with mood and psychotic disorders. We hypothesized

that lower visual memory performance would be significantly associated with the presence of psychotic symptoms.

3.3 Methods

3.3.1 Participants

We examined visual memory and psychotic symptoms in 205 participants (102 females and 103 males) from the Families Overcoming Risks and Building Opportunities for Well-Being (FORBOW) cohort. FORBOW is enriched for offspring of parents with major mood and psychotic disorders[22]. We included 7-27 year old participants who completed the RCFT and diagnostic interviews to assess psychotic symptoms and all Axis 1 disorders. We excluded participants with any known major genetic anomalies (e.g. 22q11 deletion syndrome), neurological illness (e.g. epilepsy), or intellectual disability of a degree incompatible with completing the assessments. Participants with capacity to make an informed decision provided written informed consent. For participants who could not provide informed consent, participants provided assent and a parent or guardian provided written informed consent.

3.3.2 Visual memory

Visual memory refers to the process by which visual stimuli is stored and recalled through perceptual processing, encoding, storage, and retrieval of such stimuli[33]. We assessed visual memory using RCFT. The RCFT asks participants to copy a complex figure onto a separate piece of paper and then draw the figure again from memory. In the present study, participants were asked to draw the figure from memory 3 minutes (immediate recall) and then again 30 minutes (delayed recall) after last seeing it. After the participants completed the delayed recall, they completed a recognition recall trial where they were asked to look at 24 images and identify which images were part of the original figure they copied. To ensure consistency across scoring, a single rater (EHV) scored all of the RCFTs. We used the quantitative scoring system[35] to score the RCFT. This method has been shown to have a median inter-rater reliability coefficient of 0.94[36]. Normative scores are

available for ages 6-89[35]. Consistent with previous studies[9,15], we used the delayed recall as the primary measure of visual memory.

3.3.3 Offspring psychopathology

We assessed offspring for psychiatric disorders using semi-structured interviews with offspring and their parents. For offspring ages 6-18 years, we used the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)[39] and for offspring ages 18+ years, we used the Structured Clinical Interview for DSM-5 (SCID-5)[38]. Youth assessors were separate from parent assessors and were blind to parent psychopathology. We confirmed offspring diagnoses in consensus meetings with a psychiatrist or psychologist who was blind to parent psychopathology.

3.3.4 General cognitive ability

We measured general cognitive ability using full-scale intelligence quotient (FSIQ) derived from the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II)[40] for all participants. The WASI-II FSIQ combines scores from four subtests: block design, vocabulary, matrix reasoning, and similarities. The WASI-II was administered and double scored by assessors trained in administration and scoring.

3.3.5 Psychotic symptoms

We defined psychotic symptoms as the presence of definite hallucinations or delusions reported on developmentally appropriate interview measures. We comprehensively assessed psychotic symptoms with validated instruments, including the K-SADS interview (age 6-18 years)[39], SCID-5 interview (age 18+ years)[38], Funny Feelings interview (ages 7+ years)[44,48], and the Structured Interview for Prodromal Syndromes (SIPS)[52] (ages 12+ years). These instruments consist of direct questions about the presence of hallucinations and delusions in the 12 months

prior to the interview, followed by probing to establish the content and context of each experience. We administered the semi-structured psychosis module of K-SADS or SCID-5 to all participants based on age. The Funny Feelings interview consists of seven direct questions and probes of distress, frequency, and appraisal. SIPS is a semi-structured interview designed to assess early symptoms of psychotic illness. All reported psychotic symptoms were transcribed verbatim and evaluated through curation by an independent psychiatrist or psychologist who was not involved in the assessment of the participant and was blind to parent psychopathology. Psychotic symptoms were present if they were rated as 'definite' by independent curation[44,48]. Ratings of psychotic symptoms in the year when the RCFT was administered were included in analyses.

3.3.6 Statistical analyses

To test the relationship between visual memory and psychotic symptoms, we implemented generalized linear latent and mixed models (GLLAMM)[53] logistic regression. RCFT delayed recall standard scores were used as the independent variable and psychotic symptoms as the dependent variable. We coded the presence of psychotic symptoms as yes = 1 for a participant who reported psychotic symptoms on any of the psychotic symptom measures (K-SADS, SCID-5, Funny Feelings, or SIPS) during the 12 months prior to the assessment of psychotic symptoms and administration of the RCFT. We coded this variable as no = 0 if the participant did not report psychotic symptoms in the 12 months prior to the assessment. We included sex and age as fixed effect covariates. To account for clustering of participants within families, we used the family identifier as a random effect. We conducted sensitivity analyses to ensure that our results were not unduly affected by general cognitive ability (IQ) or the presence of neurodevelopmental disorders (attention-deficit/ hyperactivity disorder (ADHD) or autism spectrum disorder (ASD)) or the presence of major depressive disorder in the offspring. We report the odds ratios (OR), their 95%

confidence intervals, and p-values. We interpreted results with p-values below 0.05 as statistically significant. All analyses were completed using STATA 15.1 software.

3.4 Results

3.4.1 Demographic and clinical characteristics

Of our participants, 10.73% reported definite psychotic symptoms within the 12 months prior to assessment. Among our 205 participants, 2 participants had a diagnosis of bipolar disorder (1 with psychotic symptoms and 1 without), 1 participant had a diagnosis of schizophrenia, and 28 participants had a diagnosis of major depressive disorder. Thus, we explored the potential role of a diagnosis of major depressive disorder on our results in sensitivity analyses. Table 3.1 presents the demographic and clinical characteristics of the participants.

Table 3.1 Demographic and clinical characteristics of youth with and without psychotic symptoms. We tested differences between groups using X^2 (for categorical variables) and t-tests (for continuous variables).

	No psychotic symptoms (n = 183)	Psychotic symptoms (n = 22)	X^2	p-value
n females (%)	94 (51.37)	14 (63.64)	1.77	0.184
Offspring diagnosis, n (%)				
ADHD	33 (18.03)	9 (40.91)	6.31	0.012
ASD	9 (4.92)	3 (13.64)	2.71	0.100
Major depressive disorder	24 (13.11)	4 (18.18)	0.43	0.513
			t-statistic	p-value
Age, mean (SD)	13.14 (4.23)	12.09 (4.28)	1.09	0.138
IQ, mean (SD)	105.60 (12.66)	105.82 (13.30)	-0.08	0.530

3.4.2 The relationship between psychotic symptoms and visual memory

We aimed to explore the relationship between psychotic symptoms in youth and visual memory performance. After accounting for age, sex, and family clustering, lower visual memory was significantly associated with the presence of psychotic symptoms (OR = 1.80, 95% CI 1.06 to 3.06, p = 0.03; Table 3.2). This suggests that youth with lower visual memory ability are more likely to experience psychotic symptoms. Figure 3 shows the means and standard errors of RCFT delayed recall scores among participants with and without psychotic symptoms.

Figure 3. The mean RCFT delayed recall standard scores for participants with and without psychotic symptoms. Error bars represent standard error of the mean.

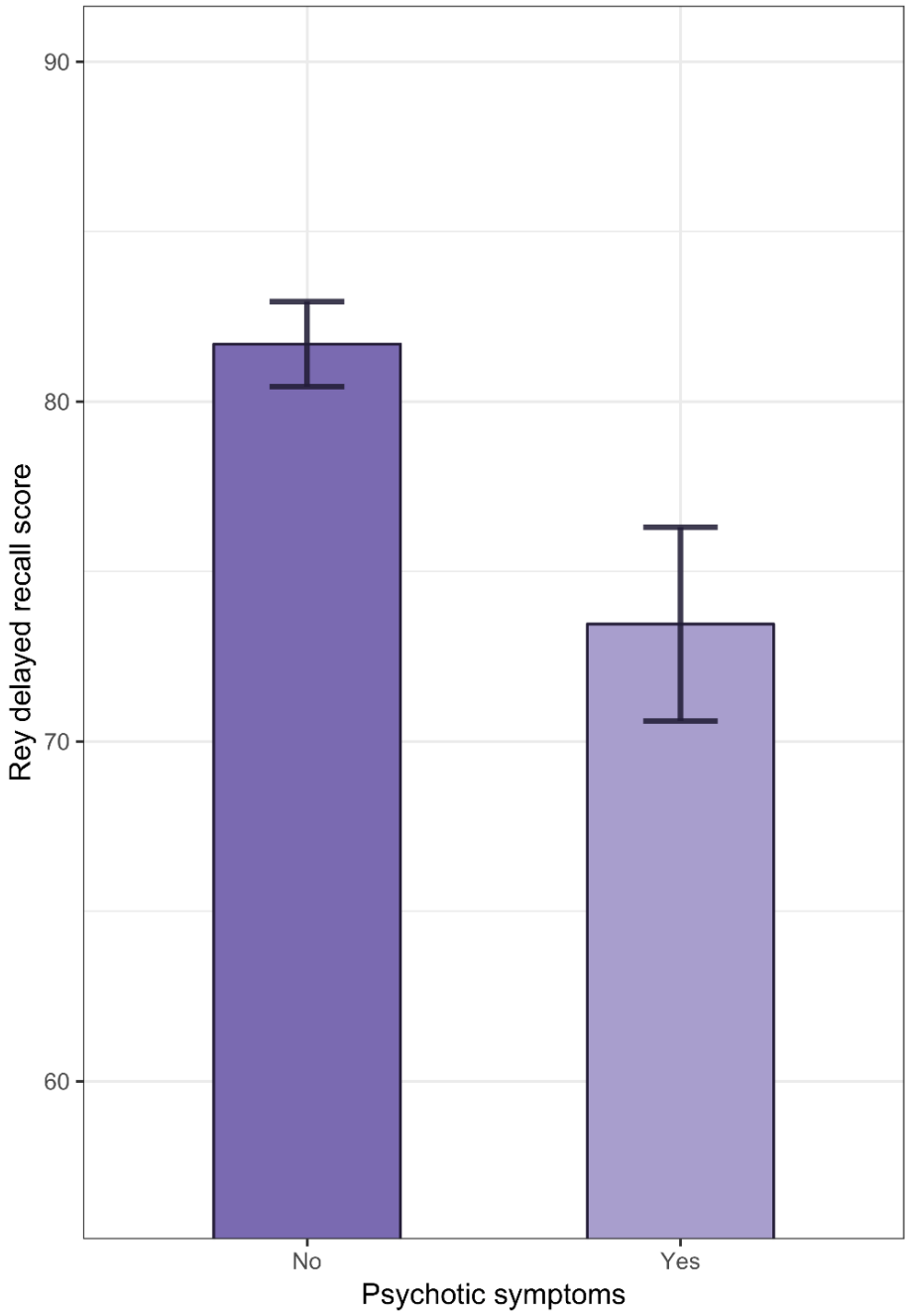


Table 3.2 Effect of psychotic symptoms on visual memory using logistic regression.

	Odds ratio	95% confidence interval lower	upper	p-value
Psychotic symptoms	**1.80**	**1.06**	**3.06**	**0.03**
Age (years)	0.93	0.83	1.05	0.25
Sex (female)	0.62	0.24	1.59	0.32
Constant	0.26	0.06	1.13	

3.4.3 Sensitivity analyses

We performed sensitivity analyses to explore whether the above result may have been affected by general cognitive ability (IQ), a diagnosis of ADHD, a diagnosis of ASD, a diagnosis of major depressive disorder, and RCFT recognition score (please refer to Tables 6 – 10 in the appendix). After accounting for sex, age, and general cognitive ability, the results remained unchanged (OR = 1.87, 95% CI 1.07 to 3.27, p-value = 0.03). When we controlled for ADHD, ASD, and major depressive disorder our results remained within one standard error of the original result (ADHD: OR = 1.70, 95% CI 1.00 to 2.89, p-value = 0.05; ASD: OR = 1.81, 95% CI 1.06 to 3.09, p-value = 0.03; Major depressive disorder: OR = 1.78, 95% CI 1.04 to 3.03, p-value = 0.04). When we accounted for RCFT recognition ability, our result was also within one standard error of the original result (OR = 1.65, 95% CI 0.92 to 2.95, p-value = 0.09).

3.5 Discussion

Prior studies have shown that psychotic symptoms in youth are associated with lower cognitive performance, including lower visual memory performance[49,50]. In the present study, we examined the relationship between visual memory performance and psychotic symptoms in a cohort enriched for offspring of parents with mood and psychotic disorders. We found that lower visual memory performance was associated with increased likelihood of experiencing psychotic symptoms. This relationship did not change when we accounted for intelligence, demonstrating that the relationship between visual memory performance and psychotic symptoms is independent of general cognitive ability.

We found that lower visual memory performance in children and youth was associated with psychotic symptoms. Previous research using questionnaire measured psychotic-like experiences reported a moderate relationship between lower visual memory performance and psychotic symptoms that was not statistically significant[49]. This apparent discrepancy may reflect the differences in quality of assessment of psychotic symptoms when using interview measures with curation by independent raters versus questionnaire measures that are likely to capture sub-clinical psychotic-like experiences. Our results are consistent with the lower visual memory ability that has been observed among individuals with first episode psychosis[13], bipolar disorder[9], schizophrenia[8], and depression[14]. Our results suggest that visual memory may represent an indicator of cognitive vulnerability to mental illness that is present among youth who are already experiencing psychotic symptoms, which is a known indicator of risk[26].

Our finding that visual memory performance is associated with psychotic symptoms in youth may have implications for both research and clinical care. This association between lower visual memory and definite psychotic symptoms measured through validated interview measures

is a novel finding. The present study is the first to use the RCFT to measure visual memory among youth with psychotic symptoms. Future studies may consider using the RCFT to assess visual memory based on its ability to discriminate between youth with and without psychotic symptoms. The difficulty of the RCFT may contribute to its ability to discriminate between youth with and without psychotic symptoms as recalling the figure also relies on other cognitive processes (e.g. constructional ability and executive functioning)[35]. Visual memory scores from the RCFT may be a useful tool for allocation to potential clinical interventions aimed at preventing mood and psychotic disorders.

The present study benefits from a large well assessed sample of offspring of parents with and without mood and psychotic disorders. Particularly, we benefit from a thorough assessment of psychotic symptoms with all participants using interview measures. This allows assessors to prompt participants to obtain more information about potential psychotic symptoms. Only psychotic symptoms rated as "definite" through independent curation by experts were used in analyses which strengthens the certainty of our findings. The RCFT was scored by one rater (EHV) allowing for consistent scoring of the RCFT throughout our sample.

However, our results should be interpreted in the context of several limitations. Most notably, our results are limited by a relatively low number of participants with definite psychotic symptoms. Thus, we had limited statistical power and our results require replication. Additionally, due to practice effects, the RCFT cannot be administered multiple times in a row. Thus, if we decided to explore repeated testing of visual memory with the RCFT[35] we would need to wait many years. The Modified Taylor Complex Figure was designed to assess similar domains for repeat testing of the RCFT and may perform similarly[43]. Future studies may examine reliability

and sensitivity of repeated measures of visual memory using different complex figures in children and adolescents.

3.6 Conclusion

In conclusion, we found that among youth, lower visual memory ability was associated with increased likelihood of experiencing psychotic symptoms. Future studies may explore the relationship between visual memory and other known risk factors for major mood and psychotic disorders. Our findings may inform future targeted early interventions for youth at risk of mood and psychotic disorders.

CHAPTER 4 GENERAL CONCLUSION

4.1 Objectives

The objective of my thesis was to explore the relationship between visual memory and risk of mental illness. Based on the potential of visual memory as an indicator of risk for mental illness[34], I aimed to explore the relationship between family history of mental illness and offspring visual memory ability. My second aim was to explore the relationship between visual memory ability in youth and psychotic symptoms, an early manifestation of risk for mental illness.

4.2 Summary of findings

First, I examined the relationship between parental mental illness and offspring visual memory. I found that increased severity of parental mental illness was associated with lower offspring visual memory ability. Second, I examined the relationship between visual memory ability and psychotic symptoms. I found that lower visual memory in youth was associated with psychotic symptoms. This finding remained robust after correcting for general cognitive ability, demonstrating the independence of visual memory measured by the RCFT from general cognitive ability.

4.3 The Developmental Risk Factor Model revisited

According to the Developmental Risk Factor Model in the context of psychosis, youth with multiple indicators of risk for psychosis should be focused on for early prevention. Murray and colleagues highlight examples of indicators of risk including genetic risk, minor psychotic symptoms, and lower cognitive performance[28]. In Chapter 2, I found that visual memory performance was associated with family history of mental illness which is a well-established risk

factor for future mental illness[20].In Chapter 3, I found that visual memory performance was also associated with the presence of psychotic symptoms in youth. Psychotic symptoms in youth is a well-established risk factor for future psychosis[44] as well as other mental illness [26]. According to the Developmental Risk Factor Model, this suggests that visual memory may be another indicator of risk to future psychosis and, in the context of our study as we used risk factors that are transdiagnostic, transdiagnostic mental illness. The complexity of the visual memory task used in this work, the RCFT, requires participants to use executive functioning, constructional ability, and perceptual reasoning skills as well as their visual memory ability in order to perform well at recalling the visually presented stimuli[35,36]. This added difficulty may allow for the RCFT to have increased ability to differentiate individuals with ranges of cognitive performance as opposed to simpler measures of visual memory that may have a ceiling effect.

4.4 Future directions

Future studies may consider using the RCFT to assess visual memory ability. We have shown that the delayed recall of the RCFT can discriminate between youth with and without psychotic symptoms and youth with and without a family history of mental illness. The RCFT can be administered quickly as it takes approximately 30 minutes complete, does not rely on language ability to complete, and can be administered to a wide range of ages[35]. Visual memory scores from the RCFT may be a useful tool for allocation to potential clinical interventions or development of targeted interventions aimed at preventing SMI.

4.5 Conclusions

I found that visual memory was associated with both parental history of mental illness and psychotic symptoms in youth. This suggests that visual memory ability in youth may be an early neurocognitive indicator of vulnerability to severe mental illness. It may be particularly

important to provide interventions and support to youth with poor visual memory and other indicators of risk for mental illness. These findings may contribute to the field of psychiatry by informing research on the developmental trajectories of severe mental illness and targeted pre-emptive interventions to prevent severe mental illness.

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APPENDIX A

Table 1. Effect of parent diagnosis on offspring visual memory using mixed-effects linear regression.

	b value	95% confidence interval lower	upper	p-value
Family history group				
Major depressive disorder	**-4.07**	**-10.47**	**2.33**	**0.213**
Bipolar disorder	**-5.04**	**-11.92**	**1.84**	**0.151**
Schizophrenia	**-11.16**	**-20.23**	**-2.08**	**0.016**
Age (years)	-0.62	-1.14	-0.10	0.020
Sex (female)	3.00	-1.56	7.55	0.197

Table 2. Sensitivity analysis controlling for general cognitive ability.

	b value	95% confidence interval lower	upper	p-value
Parent group	**-2.42**	**-5.66**	**0.83**	**0.145**
Age (years)	-0.61	-1.11	-0.12	0.015
Sex (female)	2.87	-1.45	7.18	0.193
General cognition	**0.33**	**0.16**	**0.50**	**<0.001**

Table 3. Sensitivity analysis controlling for ADHD in youth.

	b value	95% confidence interval lower	upper	p-value
Parent group	**-3.36**	**-6.60**	**-0.12**	**0.042**
Age (years)	-0.56	-1.06	-0.06	0.027
Sex (female)	2.90	-1.54	7.33	0.200
ADHD	**-3.21**	**-8.79**	**2.37**	**0.260**

Table 4. Sensitivity analysis controlling for autism spectrum disorders in offspring.

	b value	95% confidence interval lower	upper	p-value
Parent group	**-3.57**	**-6.79**	**-0.35**	**0.030**
Age (years)	-0.55	-1.05	-0.05	0.031
Sex (female)	3.26	-1.19	7.71	0.151
ASD	**-0.47**	**-10.93**	**9.99**	**0.930**

Table 5. Sensitivity analysis controlling for RCFT recognition

	b value	95% confidence interval lower	upper	p-value
Parent group	**-2.77**	**-5.60**	**0.07**	**0.056**
Age (years)	-0.57	-1.02	-0.12	0.012
Sex (female)	4.86	0.87	8.86	0.017
Recognition	**0.38**	**0.28**	**0.49**	**<0.001**

Table 6. Sensitivity analysis controlling for general cognitive ability.

	Odds ratio	95% confidence interval lower	upper	p-value
Psychotic symptoms	**1.87**	**1.07**	**3.27**	**0.03**
Age (years)	0.93	0.83	1.05	0.24
Sex (female)	0.69	0.27	1.80	0.45
General cognition	**1.01**	**0.98**	**1.05**	**0.43**
Constant	0.05	>0.01	3.24	

Table 7. Sensitivity analysis controlling for ADHD in youth.

	Odds ratio	95% confidence interval lower	upper	p-value
Psychotic symptoms	**1.70**	**1.00**	**2.89**	**0.05**
Age (years)	0.93	0.83	1.06	0.29
Sex (female)	0.74	0.28	1.97	0.55
ADHD	**2.57**	**0.97**	**6.84**	**0.06**
Constant	0.18	0.04	0.89	

Table 8. Sensitivity analysis controlling for autism spectrum disorders in youth.

	Odds ratio	95% confidence interval lower	upper	p-value
Psychotic symptoms	**1.81**	**1.06**	**3.09**	**0.03**
Age (years)	0.93	0.82	1.04	0.20
Sex (female)	0.71	0.27	1.87	0.49
ASD	**2.86**	**0.65**	**12.64**	**0.17**
Constant	0.25	0.06	1.11	

Table 9. Sensitivity analysis controlling for major depressive disorder in youth.

	Odds ratio	95% confidence interval lower	upper	p-value
Psychotic symptoms	**1.78**	**1.04**	**3.03**	**0.04**
Age (years)	0.89	0.77	1.03	0.12
Sex (female)	0.61	0.24	1.58	0.31
Major depressive disorder	2.72	0.60	12.27	0.19
Constant	0.41	0.08	2.13	

Table 10. Sensitivity analysis controlling for RCFT recognition.

	Odds ratio	95% confidence interval lower	upper	p-value
Psychotic symptoms	**1.65**	**0.92**	**2.95**	**0.09**
Age (years)	0.94	0.84	1.05	0.27
Sex (female)	0.60	0.23	1.55	0.29
Recognition	**1.16**	**0.71**	**1.91**	**0.55**
Constant	0.25	0.06	1.10	