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**Neural correlates of memory dysfunction across stages of schizophrenia-
spectrum disorder**

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Melbourne Neuropsychiatry Centre, Department of Psychiatry

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Abstract

Schizophrenia-spectrum disorders are severe mental illnesses characterised by hallucinations, delusions, blunted affect and disorganised thought patterns. A core feature of these disorders is cognitive deficits, which are associated with functional disability. Episodic memory, in particular, is one of the most severely impacted areas of cognitive functioning in schizophrenia-spectrum disorder, and memory deficits predict poorer clinical prognosis and increased functional disability. However, the longitudinal course of episodic memory deficits in schizophrenia-spectrum disorders is currently poorly defined, with the focus to date being on areas of functioning that are already impaired in early illness stages, such as verbal memory. In order to better understand trajectories, it may be important to examine areas of functioning that are preserved early in the illness, such as visual associative memory. Furthermore, there is currently a poor understanding of the neural underpinnings of memory impairment in schizophrenia-spectrum disorders, making it difficult to develop targeted interventions aimed at ameliorating these deficits. It is plausible that episodic memory impairments in these disorders is related to underlying dysfunction in the brain regions and networks that underlie this ability – namely, the hippocampus and its connections to the prefrontal cortex.

This thesis utilised longitudinal cognitive assessment and cross-sectional multi modal neuroimaging to address three primary research aims:

1. To investigate the longitudinal course of episodic memory ability over a 5-11-year follow-up period in individuals with first-episode psychosis.
2. To investigate relationships between visual associative memory performance and hippocampal subfield volumes in FEP individuals and individuals with chronic schizophrenia-spectrum disorders.
3. to investigate whether visuospatial associative memory ability is related to white matter microstructure in the hippocampal-prefrontal pathway in FEP individuals and individuals with chronic schizophrenia-spectrum disorders.

Results showed that visual associative memory ability was preserved in individuals who had recently experienced a first psychotic episode, but deteriorated over a 5-11 year follow-

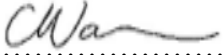
up period. Conversely, verbal associative memory ability improved over the follow-up period to the same degree in FEP individuals and healthy controls. In a subsequent cross-sectional study, we found that, while hippocampal subfield volume reductions were present only in individuals with chronic schizophrenia-spectrum disorder, poorer episodic memory performance was associated with reduced subfield volumes in the CA4/dentate gyrus (DG) and in the stratum layers in both FEP individuals and those with chronic schizophrenia-spectrum disorder. Finally, we found that abnormal white matter microstructure in a number of memory-related ROIs and hippocampal-prefrontal pathways was present only in individuals with chronic schizophrenia-spectrum disorder. Furthermore, microstructural abnormalities in the fornix and the hippocampal-thalamic pathway were associated with poorer memory performance in individuals with chronic schizophrenia-spectrum disorder, but not FEP individuals. These findings provide new insights into the neural underpinnings of episodic memory impairment across stages of schizophrenia-spectrum disorder, and suggest that hippocampal structure may be more relevant to memory impairment in FEP individuals, with memory-related white matter abnormalities emerging in later illness stages.

Declaration

This is to certify that:

- i) The thesis comprises only my original work towards the PhD, except where indicated
- ii) Due acknowledgement has been made in the text to all other material used,
- iii) The thesis is less than 100,000 words in length, exclusive of tables, figure legends, bibliography and appendices.

Cassandra Wannan

Signature:.....

Date:

30/11/2020

Preface

I am the sole first author of all three studies presented in this thesis. For all three studies, I have been the most significant contributor to all study components, including conceptualisation of the research question, experimental design, image processing, statistical analysis and manuscript preparation and dissemination in accordance with The University of Melbourne's doctoral thesis outlines. For studies 4 and 5, I was also involved in participant recruitment and assessment.

The work in *Chapter 3* was published in the journal *Psychological Medicine* in December 2018. Data for this study were collected as part of a wider study conducted by Orygen Youth Health's Early Psychosis Prevention and Intervention Centre (EPPIC). I would like to thank Patrick McGorry and Christos Pantelis for allowing me to use the cognitive data collected for this study. This work was presented at the Australasian Schizophrenia Conference in Melbourne, Australia, September, 2015

The work in *Chapter 4* was published in the journal *Psychological Medicine* in October 2019. The data used in this chapter was collected as part of two wider studies: the Microglial Study, and the Collaborative Research Centre (CRC) for Mental Health Study. The Microglial Study. I would like to acknowledge and thank Vanessa Cropley and Christos Pantelis for allowing me to use the MRI and cognitive data collected for these studies. I would also like to thank our research assistant Steven Tahtalian, who was primarily involved in screening, assessing and scanning participants. This work was presented at the Schizophrenia International Research Society Conference in April 2019, Orlando, Florida, USA.

The work in *Chapter 5* has been submitted to the journal X for publication. This study also utilised data from the Microglial Study and the CRC for Mental Health Study. I would like to thank Andrew Zalesky and Maria di Biase for their help with diffusion image processing and troubleshooting. This work was presented at the Schizophrenia International Research Society Conference in April 2019, Orlando, Florida, USA.

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I am also indebted to my amazing team of supervisors, who have been nothing but supportive throughout my candidature. Dr Cali Bartholomeusz, you took a chance on someone who had been working in a different field for several years, and I am so grateful for the opportunity you gave me. I have truly appreciated your ability to keep me focused and all of the invaluable feedback you have given me over the past few years – I can't thank you enough for your support and would not have reached this milestone without you. Dr Vanessa Cropley, you have been both a mentor and a friend, offering me guidance in so many different aspects of my professional life that I will use for years to come. I am incredibly grateful for all of my "quick questions" that turned into 40-minute conversations about science, academia, working relationships, and life, and hope that someday I am able to provide the same support for a student of my own. Prof Christos Pantelis, you have given me so many opportunities to contribute to various projects throughout my PhD, and have always been incredibly supportive of me following my interests. It is such an important thing as a PhD student to feel as though someone believes in your abilities, especially when that person has so many years of experience and so much passion for research themselves. A special mention also to A/Prof Andrew Zalesky, who provided such expert guidance and analytical support for my AJP paper, and also went out of his way to help me with my white matter data processing and analysis. It was a pleasure working together and hope that we can collaborate again in the future.

I would also like to acknowledge everyone at Melbourne Neuropsychiatry Centre who has contributed to creating such an amazing, collaborative work environment. To my fellow students, I am so grateful for all of the lunches we have had together, the student retreats and monthly SONR meetings. It had been an honour to grow together as researchers and friends. In particular, my PhD sister, Ellie Ganella – I don't quite have the words to express how much your friendship and support has meant to be since we started together back in 2014. We have been through just about every life event you could imagine together, and I miss seeing

you at MNC every day. I don't know how I got lucky enough to have you beside me on the PhD roller coaster, but I am so very thankful for your presence in my life, the endless chats, the coffee and tea dates, all of the food, and all of the laughs. And a special mention to a few other people who have not only been colleagues but also friends over the past few years – James, Lily, and Tammy. We may have spent longer chatting

To my wonderful friends and family, who have been nothing but supportive throughout my PhD – thank you. Mum and Dad, for the weeks I spent at your house during maternity leave so I could work on publications and get my thesis finished, I will forever be grateful. Mum in particular, there's no way I could have finished this thing without your time and your willingness to spend 3 hours in the car each week to look after Izzy. And to my sisters, Felicity and Elizabeth, thank you for being my cheerleaders and for always being there when I needed a break from work. And my second family – Judy, Steve, Zach, and Kobe – thank you for always being supportive, and for always asking how my PhD was going. And last, but certainly not least, my biggest thanks are reserved for my amazing husband, Xander, and my incredible daughter, Isabel. Xander, your support throughout my PhD has been unwavering and I would never have made it to the finish line without you. You have encouraged me every step of the way, whether it was working at the lab until 8pm for months on end, or travelling to Canada for a month to visit a lab – you never hesitated to tell me to go for it. I am so lucky to have had you by my side throughout this journey. And Isabel, you have made every moment away from my PhD a joy. I will always remember you, at almost two years old, saying “I love the beautiful brain inside your head, mummy!” Your first lessons in neuroscience have clearly paid off.

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List of publications

First author articles resulting from this thesis:

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Mostaid, M. S., Dimitrakopoulos, S., **Wannan, C.M.J.**, Cropley, V., Weickert, C. S., Everall, I., Pantelis, C., Bousman, C. (2018). An Interleukin-1 beta (IL1B) haplotype linked with psychosis transition is associated with IL1B gene expression and brain structure. *Schizophrenia Research*.

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Abbreviations

AD	Axial diffusivity	NART	National Adult Reading Test
ANCOVA	Analysis of covariance	NMDA	N-methyl-D-aspartate
BPRS	Brief Psychiatric Rating Scale	PAL	Paired-Associates Learning
CA	Cornu ammonis	PANSS	Positive and Negative Syndrome Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery	PR	Pattern Recognition
CPZ	Chlorpromazine	RD	Radial diffusivity
DG	Dentate gyrus	ROI	Region of interest
DOI	Duration of illness	SANS	Scale for the Assessment of Negative Symptoms
DSM	Diagnostic and Statistical Manual	SCID	Structured Diagnostic Interview for DSM
DTI	Diffusion tensor imaging	SOFAS	Social and Occupational Functioning Assessment Scale
DWI	Diffusion weighted imaging	SRLM	Stratum radiatum-lacunosum-moleculare
EPPIC	Early Psychosis Prevention and Intervention Centre	SSD	Schizophrenia-spectrum disorders
FA	Fractional anisotropy	TBSS	Tract-based spatial statistics
FDR	False discovery rate	UF	Uncinate fasciculus
FEP	First-episode psychosis	UHR	Ultra-high risk
HC	Healthy controls	VPA	Verbal Paired Associates
ICV	Intracranial volume	WAIS-R	Wechsler Adult Intelligence Scale-Revised
MD	Mean diffusivity	WM	White matter
MINI	Mini International Neuropsychiatric Interview	WMS-R	Wechsler Memory Scale Revised
mPFC	Medial prefrontal cortex	WTAR	Wechsler Test of Adult Reading
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient Echo		
MRI	Magnetic resonance imaging		

CHAPTER 1:

General Introduction

1. 1. Schizophrenia-spectrum disorders

1.1.1. Epidemiology

The most common form of psychotic illness is schizophrenia, which has a lifetime prevalence of approximately 1% throughout the world (Doherty and Owen, 2014). Schizophrenia, along with other less common psychotic illnesses such as schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, psychosis not otherwise specified, or delusional disorder, are often included under the umbrella term of schizophrenia-spectrum disorders. In Australia, the prevalence of psychotic illnesses is estimated to be around 1.5%, with the greatest number of cases observed in males aged 25-34 (Morgan *et al.*, 2010). Schizophrenia-spectrum disorders account for approximately 1.2% of total health expenditure in Australia, with the annual economic cost of the disorder, which includes damages such as those associated with mortality, morbidity, health costs, lost workplace productivity, crime and legal costs, being estimated at approximately \$4.91 billion (Neil *et al.*, 2014).

The disease burden for individuals with schizophrenia-spectrum illness is also high, with these disorders often having a devastating impact on those diagnosed and their families. Schizophrenia is among the world's top ten causes of long-term disability (Mueser and McGurk, 2004), with illness onset associated with a steep decline in socioeconomic status and employment rates (Hakulinen *et al.*, 2019). In Australia, 85% of individuals living with a psychotic illness reported that their main source of income was government pensions, and only one-third of individuals were engaged in any type of employment (Morgan *et al.*, 2010). Individuals with schizophrenia also have a substantially reduced life expectancy relative to the general population, living 10-20 years less on average (Laursen *et al.*, 2014). This reduction in life expectancy is caused by a range of factors, including suicide, cardiovascular disease, substance abuse, and diabetes (Leucht *et al.*, 2007).

Schizophrenia-spectrum disorder typically emerges during late adolescence or early adulthood, with peak periods of onset between the ages of 15 and 25 in men and 18 and 30 in women (Sutterland *et al.*, 2013), although women are known to experience a second peak in the onset of the disorder following menopause (Stilo and Murray, 2010). While the lifetime incidence of schizophrenia-spectrum disorder is thought to be relatively equal among men and women (although some studies suggest a slightly higher incidence in males), women tend to have a milder illness course than men, characterised by fewer hospitalisations and better social functioning (Mueser and McGurk, 2004).

1.1.2. Symptoms

Schizophrenia-spectrum disorders are severe and debilitating mental disorders, characterised by high inter-individual variability in symptoms (Andreasen, 2000). The symptomatology of schizophrenia, considered the more severe of the schizophrenia-spectrum disorders is complex and encompasses multiple domains, including positive, negative, disorganization, cognitive, mood and motor symptoms (Battle, 2013). Of these domains, positive and negative symptoms are often considered to be the most characteristic of schizophrenia. Positive symptoms represent added unnatural functions, and include perceptual abnormalities, such as auditory and visual hallucinations, and delusions. Conversely, negative symptoms are characterised by the loss or diminution of certain normal functions, and include symptoms such as affective flattening, alogia, anhedonia, and avolition. Additionally, while they are not included in the diagnostic criteria for schizophrenia-spectrum illness, cognitive symptoms, such as impairments in memory, attention, and executive functioning, are increasingly considered to be a core symptom of the disorder (Kahn and Keefe, 2013).

A common tool used for diagnosing schizophrenia-spectrum disorders is the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Based on DSM-V criteria, a diagnosis of schizophrenia is given if two of the following symptoms are present for a significant portion of time during a 1-month period; hallucinations, delusions, disorganized speech, disorganised or catatonic behaviour and negative symptoms.

Additionally, these symptoms must be accompanied by functional deterioration in one or more major areas, such as work, interpersonal relations, or self-care. Continuous signs of the disturbance must persist for at least 6 months, and this period must include at least 1 month of symptoms. Individuals with schizoaffective disorder must meet the criteria for schizophrenia, but also have an uninterrupted duration of illness during which there is a major mood episode (manic or depressive). While schizophrenia and schizoaffective disorder are the most common schizophrenia-spectrum disorders, a number of other diagnoses fall under this umbrella term, as mentioned above. Individuals with first-episode psychosis (FEP), in particular, may be diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, affective spectrum psychoses (i.e., bipolar disorder with psychotic features, major depressive disorder with psychotic features), delusional disorder, acute and transient psychotic disorder/brief psychotic disorder, substance/medication-induced psychotic disorder, or unspecified schizophrenia spectrum and other psychotic disorder (Fusar-Poli *et*

al., 2016). The diagnostic stability of schizophrenia and schizoaffective disorders in FEP individuals is high, whereas other schizophrenia-spectrum diagnoses, such as acute and transient psychotic disorder/brief psychotic disorder, psychosis not otherwise specific, and schizophreniform disorder are less stable, often shifting to a schizophrenia diagnosis over a follow-up period (Fusar-Poli *et al.*, 2016).

1.1.4. Treatment of schizophrenia-spectrum disorders

The introduction of the dopamine D2 antagonist chlorpromazine (CPZ) in the 1950's constitutes a major breakthrough in the treatment of schizophrenia. Following the discovery of chlorpromazine, a number of other first-generation, or typical, antipsychotics were soon developed, beginning with haloperidol (Cunningham Owens and Johnstone, 2018). However, while typical antipsychotics showed promise in treating the positive symptoms of schizophrenia, they were not effective in ameliorating negative symptoms. Additionally, due to their high affinity for the dopamine receptor, they often produced extrapyramidal side-effects, including tardive dyskinesias, Parkinsonism, akathisia, and dystonias (Mathews *et al.*, 2005). Due to their high affinities for histamine H1 receptors, muscarinic M1 receptors, and α adrenergic NE α 1 receptors, some typical antipsychotics also caused worsening of cognitive deficits (Hill *et al.*, 2010). Second-generation, or atypical, antipsychotics generally have a lower affinity for the dopamine receptor and also block serotonin receptors, resulting in fewer extrapyramidal side-effects. The first atypical antipsychotic was clozapine, which showed promise in treating the positive symptoms of schizophrenia, but was also associated with potentially life-threatening cardiac side-effects (Khan *et al.*, 2017). Thus, clozapine is reserved for use with individuals whose illness does not respond to other antipsychotic medications. Subsequently, a number of other atypical antipsychotic medications have been developed, with varying levels of affinity for different receptors, such as dopamine, serotonin, muscarinic, and adrenergic (Cunningham Owens and Johnstone, 2018). It was hoped that atypical antipsychotics would show increased potential for treating the cognitive symptoms of schizophrenia-spectrum disorder relative to typical antipsychotics, however these hopes have largely not been realised (Hill *et al.*, 2010). Similarly, while atypical antipsychotic medications can be effective for ameliorating positive symptoms, they have limited efficacy for alleviating negative symptoms (Webb and Tandon, 2009; Remington *et al.*, 2016).

Antipsychotic medications are typically used in conjunction with psychotherapy, and a

number of cognitive and sociotherapeutic approaches have been developed to target some of the functional disabilities associated with the disorder. One of the most effective forms of non-pharmacological treatment for schizophrenia is cognitive behavioural therapy, which appears to target both the positive and negative symptoms (Tai and Turkington, 2009), and shows efficacy for individuals who do not respond to antipsychotic medication (Burns *et al.*, 2014). However, even with advances in antipsychotic medication and psychotherapeutic techniques, schizophrenia-spectrum disorders are often still associated with a poor prognosis, with only a small minority of individuals who experience a FEP going on to achieve sustained recovery, and a substantial proportion going on to develop either recurring or non-remitting illness (Lappin *et al.*, 2018).

1.1.4. The clinical staging model

As with other severe mental illnesses, psychotic disorders typically evolve over time to become more severe and more distinct in terms of clinical presentation as the illness progresses (McGorry *et al.*, 2014). Thus, a clinical staging model is often used to differentiate individuals at earlier illness stages from those with a more chronic or severe form of psychosis (see Figure 1.1). In particular, a distinction is often made between individuals who are considered to be in the putative prodrome, individuals who have experienced a first full-threshold psychotic episode, and those who have a chronic, recurring form of the illness. A clinical staging model is advantageous as it allows clinicians to select treatment options most relevant to an individual's illness stage, and it encourages early identification and intervention strategies, potentially leading to more positive outcomes for individuals experiencing psychosis (McGorry *et al.*, 2014).

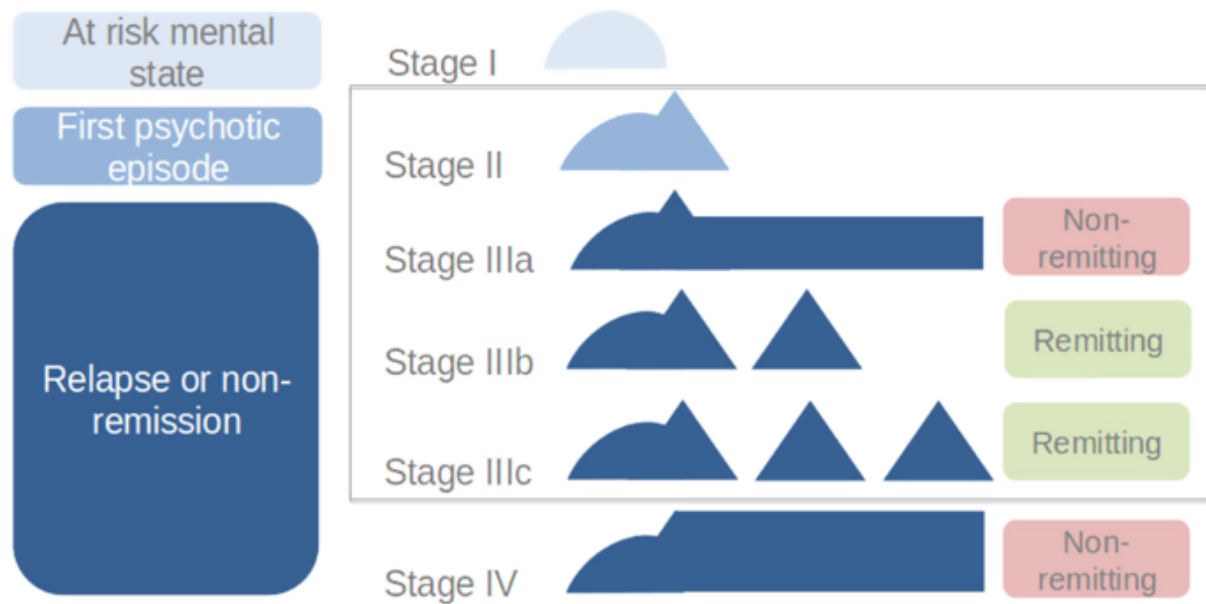


Figure 1.1. Schematic representation of the clinical staging model. Sourced from Griffa et al. (2019)

The prodromal stages of psychotic illness are typically characterised by mild, often undifferentiated general symptoms, including sub-threshold psychotic symptoms, cognitive impairment, and mood and anxiety symptoms, that increase in syndromal specificity over time (Yung and McGorry, 1996; McGorry *et al.*, 2014). An individual whose psychotic symptoms have not yet reached the frequency or severity required for a diagnosis of a schizophrenia-spectrum disorder, are often described as being at ultra-high risk (UHR) for developing psychosis (McGorry *et al.*, 2003). The UHR definition also includes individuals who have a genetic risk (i.e. first degree relative with a psychotic disorder or schizotypal personality) for schizophrenia and a decline in functioning (Yung *et al.*, 2005). Current estimates suggest that the rate of transition from the UHR state to a clinically diagnosed psychotic disorder is between 20% and 40% (Fusar-Poli, 2012; Goulding *et al.*, 2013; Clark *et al.*, 2015). While the UHR stage of psychosis is a rapidly growing area of research, it is also worth noting that viewing the high-risk state as a potential precursor to developing a schizophrenia-spectrum disorder has been criticised for a number of reasons (van Os and Guloksuz, 2017). Identifying UHR individuals can be incredibly difficult, and a recent study of 338 FEP individuals attending a mental health service found that only 4.1% of these individuals were true UHR cases who had prior contact with a prodromal clinic (Ajnakina, 2016). Additionally, sub-threshold psychotic symptoms may be present across a range of psychiatric disorders, including but not limited to anxiety, depression, eating disorders, post-traumatic stress disorder, attention-deficit/ hyperactivity disorder, and substance use disorders

(Linscott and Van Os, 2013). Importantly, meta-analysis revealed that only 7.4% individuals with baseline psychotic experiences went on to develop a psychotic disorder over a follow-up period (Linscott and Van Os, 2013). In non-psychotic disorders, the presence of attenuated psychotic symptoms has been shown to be associated with poorer response to treatment and greater illness severity (Perlis *et al.*, 2011; Kelleher *et al.*, 2012; Wigman *et al.*, 2012, 2014), and it is therefore possible that the UHR stage is a marker for poor prognosis across a range of psychiatric illnesses, not only schizophrenia-spectrum disorder.

The onset of full-threshold psychotic symptoms is typically referred to as first-episode psychosis. In order to be diagnosed with FEP, two of the following symptoms must be present for at least one month: hallucinations, delusions, disorganised or catatonic behaviour and/or negative symptoms, with enduring signs of functional deterioration (i.e. occupational, social, or cognitive dysfunction) present for at least six months (Battle, 2013). An individual's first full-threshold psychotic episode typically occurs during their late teens or early twenties, and, while some individuals may recover symptomatically from the first episode, a substantial number (~40-80%) will go on to develop a more chronic form of psychotic disorder characterised by symptomatic relapses, treatment failure and incomplete recovery, and prolonged illness (Lambert *et al.*, 2008; Ventura *et al.*, 2011).

Given that maximal disability is reached within 5 years after illness onset, the early stages of psychosis, which include both UHR and FEP, are considered to be a critical period in terms of intervening early in order to minimise the degree of functional disability (Birchwood *et al.*, 1998; McGorry *et al.*, 2008; Bartholomeusz *et al.*, 2016). Data from Australia indicate that following a first psychotic episode, over 90% of patients will experience further psychotic episodes, with approximately 20% of patients experiencing continuous illness with unremitting symptoms (Morgan *et al.*, 2010).

1.2. Aetiology and neuropathology of schizophrenia-spectrum disorders

1.2.1. Aetiology

Schizophrenia-spectrum disorders are disorders whose cause or causes remain unknown, however, it is generally agreed that a combination of genetic and environmental factors underlies the onset of the disorder (Mueser and McGurk, 2004). These genetic and environmental factors may interact to result in the pathophysiological changes and manifestations associated with the illness (van Os *et al.*, 2014). Twin studies provide

evidence that genetic liability plays a large role in the aetiology of schizophrenia, with current heritability estimates sitting around 80% (Cannon *et al.*, 1998; Sullivan *et al.*, 2003; Hilker *et al.*, 2018). However, despite the high heritability of the disorder, the actual genetic architecture underlying the illness is complex and poorly understood (Gejman *et al.*, 2010). Schizophrenia is thus considered to be a complex genetic disorder, with many genes thought to confer only a small effect – approximately seven percent – on the phenotype (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). A number of environmental risk factors, both prenatal and postnatal, have also been shown to contribute to the development of psychotic disorders, and these include advanced paternal age, prenatal infection or other health complications (e.g. preeclampsia, diabetes, rhesus incompatibility), season of birth, obstetric complications, childhood trauma, early life stress and maternal separation, social isolation, urban living environment and migration (McGrath *et al.*, 1997; Dean and Murray, 2004; Stilo *et al.*, 2011).

1.2.2. Neural basis of schizophrenia-spectrum disorders

Schizophrenia is considered to be a disorder of the brain and mind, and this conceptualisation of the disease has existed since early descriptions of the disease proposed by Emile Kraepelin and Eugen Bleuler. Numerous studies provide evidence for disturbances in both brain structure and function in schizophrenia-spectrum disorders, with the advent of magnetic resonance imaging (MRI) allowing researchers to explore the neurobiological underpinnings of these disorders in-vivo. In line with the clinical staging model, these abnormalities appear to occur in a stage-dependent manner, with more severe abnormalities present in individuals in more chronic illness stages (Karlsgodt *et al.*, 2010; Torres *et al.*, 2016; Wannan *et al.*, 2019). Consistent with these cross-sectional findings, longitudinal studies in early illness stages have shown that abnormal brain development occurs predominantly in the years immediately following psychosis onset (Bartholomeusz *et al.*, 2016).

Meta-analyses of structural brain abnormalities in schizophrenia-spectrum disorders reveal consistent increases in ventricular volume and reductions in whole brain volume (Wright *et al.*, 2000; Haijma *et al.*, 2013). Grey and white matter abnormalities have also been observed across a range of cortical and subcortical regions. In particular, prominent volume reductions are present in the hippocampus and thalamus relative to healthy individuals, and reductions in cortical grey matter are present to the largest extent in the prefrontal cortex, temporal lobes, cingulate cortex and insula (Wright *et al.*, 2000; Fornito *et al.*, 2009; Sun *et al.*, 2009b;

Takahashi *et al.*, 2009b, 2009a; Bora *et al.*, 2011; Haijma *et al.*, 2013). Abnormalities in these regions are typically observed in both early and established illness – although the degree tends to be greater in those in later illness stages, and cortical abnormalities also extend posteriorly to parietal and occipital regions to a greater extent in individuals with more chronic illness (Cropley *et al.*, 2017; Wannan *et al.*, 2019). White matter deficits are also observed in frontal and temporal regions in individuals with schizophrenia-spectrum disorders (Ellison-Wright and Bullmore, 2009; Bora *et al.*, 2011; Haijma *et al.*, 2013), and these regions contain tracts that link many of the cortical and subcortical regions implicated in these disorders. Further, recent evidence supports the notion of a direct link between findings in grey- and white-matter pathology in schizophrenia-spectrum disorders (Di Biase *et al.*, 2019).

1.2.3. Neurodevelopmental vs. neuroprogressive processes in schizophrenia-spectrum disorders

Attempts to understand brain changes in schizophrenia require that these changes be placed in the context of brain maturational processes from childhood to adolescence. Although basic cognitive skills are acquired by early adulthood, the human brain continues to develop throughout adolescence and into early adulthood (Sowell *et al.*, 2003). Longitudinal reductions in grey matter density as part of normal neurodevelopment have been observed in healthy individuals up until the mid-twenties (Gogtay *et al.*, 2004), while white matter volumes have been found to increase up to the third decade of life (Yakovlev and Lecours, 1967; Pfefferbaum *et al.*, 1994; Sowell *et al.*, 2003; Gogtay *et al.*, 2011). The brain regions that appear to undergo the most significant structural and functional changes during adolescence, are those that are closely associated with the regulation of behaviour and emotion, and the evaluation of risk and reward (Steinberg, 2005). Higher-order cognitive abilities are also developing during this period, with refinements observed in domains such as executive functions and verbal skills (De Luca *et al.*, 2003; Paus, 2005). These brain and behavioural changes are also occurring at a time when individuals are typically experiencing significant psychosocial changes, such as in family and peer relationships, developing their personal identity, and experiencing the hormonal changes associated with puberty (Steinberg and Morris, 2001; Paus *et al.*, 2008). It has been suggested that this combination of factors may lead to an increased vulnerability to mental disorders in this age group (Paus *et al.*, 2008), which is evidenced by the peak onset of psychotic disorders occurring during adolescence and early adulthood.

Kraepelin's original conceptualisation of dementia praecox suggested that psychotic illness was the result of premature and progressive brain degeneration (Seidman *et al.*, 2010). However, the current dominant notion is that schizophrenia is a disorder of neurodevelopmental origin (Pantelis *et al.*, 2003, 2005; Forsyth and Lewis, 2017). The neurodevelopmental model of schizophrenia, proposed separately by Weinberger (1987) and Murray and Lewis (1987), posits that abnormal neurodevelopmental processes are the underlying cause of psychotic illnesses. Specifically, a prenatal or perinatal insult confers a predisposition for the development of psychotic illness, and later brain maturational processes or other stressors 'trigger' the onset of illness (Weinberger, 1987). The notion originally proposed by Weinberger (1987) was of a static lesion that was postulated to affect brain development relevant to brain regions implicated in schizophrenia. More recently, this idea was challenged and further elaborated to suggest that the neurodevelopmental timing of a lesion was important to the features of schizophrenia observed, which may also provide a way to understand the heterogeneity of brain changes observed in schizophrenia (Pantelis *et al.*, 2005). Thus, the manifestation of a neurological insult will depend on the individual's stage of brain development at the time when it occurs, with a relatively greater impact observed for brain structures and functions that are maturing around the time of illness onset (Pantelis *et al.*, 2003, 2005; Gogtay *et al.*, 2011; Rapoport *et al.*, 2012). This model provides a framework for understanding the trajectories of different brain functions in psychotic illness based on their typical developmental course (Testa and Pantelis, 2009; Cropley and Pantelis, 2014). Areas of functioning that undergo their maturational processes prior to illness onset are likely to follow a relatively normal developmental trajectory and may be preserved in individuals with psychosis (Pantelis *et al.*, 2009b, 2009c, 2015). Conversely, disruption of functioning will be maximal for those abilities that should be continuing to develop but are disrupted by the onset of illness. Such developmental arrest would be expected to result in impairments that are observable even in the earliest illness stages and that remain stable over time. Such a notion is consistent with findings that earlier age of illness onset is associated with a more severe illness course, characterised by more frequent hospitalisation, increased negative symptoms, poorer social and occupational functioning, poorer global outcomes, and more severe cognitive deficits in individuals with a schizophrenia-spectrum disorder (Rajji *et al.*, 2009; Immonen *et al.*, 2017).

However, one criticism of the neurodevelopmental model is that, although it can explain stable deficits, it may not account for the deterioration of brain structure or functioning that is often seen over the course of psychotic illness (Woods, 1998). In schizophrenia, there is a clear deterioration in mental state as the illness progresses from the prodrome through to more chronic illness stages (McGorry *et al.*, 2014). Furthermore, individuals with schizophrenia exhibit an accelerated rate of grey and white matter loss compared to healthy individuals, suggestive of premature brain aging (Fusar-Poli *et al.*, 2012; Zhang *et al.*, 2015b; Cropley *et al.*, 2017). Recent evidence also suggests that performance in some areas of cognitive ability may also deteriorate in the early stages of psychosis, and that elderly patients with schizophrenia (aged 65 and above) demonstrate a decline in cognitive functioning over and above what would be expected as the result of normal aging (Pantelis *et al.*, 2009a; Seidman *et al.*, 2010; Harvey, 2014). Thus, it is possible that neurodegenerative processes are occurring alongside the neurodevelopmental abnormalities that are typically thought to take place in psychotic illnesses, consistent with Kraepelin's original conceptualisation of schizophrenia as a disorder of brain degeneration. Despite these criticisms, it is also possible that progressive brain abnormalities observed in schizophrenia-spectrum disorder reflect accelerated brain neurodevelopment during adolescence and early adulthood, and are thus consistent with the neurodevelopmental hypothesis (Sun *et al.*, 2009b, 2009a; Cropley *et al.*, 2017). Thus, normal developmental processes such as synaptic pruning may be accelerated in individuals with schizophrenia-spectrum disorder, leading to accelerated grey matter volume decline (Feinberg, 1982; Boksa, 2012).

Currently it is difficult to disentangle potential neurodegenerative and neurodevelopmental processes in schizophrenia-spectrum disorder, however, regardless of the underlying mechanisms, it is clear that these processes lead to progressive brain abnormalities as the disorder progresses. What is more contentious is whether these processes might also lead to cognitive decline in individuals with a schizophrenia-spectrum disorder.

1.3. Cognition and memory in schizophrenia-spectrum disorders

1.3.1. Cognitive impairment in schizophrenia-spectrum disorders

Cognitive deficits are considered to be a core feature of schizophrenia-spectrum disorders, and mild impairments on cognitive measures and academic performance are evident years before the onset of clinical symptoms (Heinrichs and Zakzanis, 1998; Bilder *et al.*, 2006; Seidman *et al.*, 2010; Mollon and Reichenberg, 2018; Sheffield *et al.*, 2018; Dickson *et al.*,

2020). In individuals with a chronic schizophrenia-spectrum disorder, deficits have been identified across virtually all cognitive domains, with the greatest levels of impairment observed in attention, executive function, speed of information processing and memory (Heinrichs and Zakzanis, 1998; Bora *et al.*, 2009; Fioravanti *et al.*, 2012; Allott, 2019). Deficits are also observed in a number of social cognition domains, including emotion processing, mentalizing and social perception (Green *et al.*, 2019). The level of neuropsychological impairment in individuals with a schizophrenia-spectrum disorder has been found to be between one and two standard deviations below the mean of healthy comparison groups (Keefe *et al.*, 2011), suggestive of mild to moderate cognitive impairment. Milder impairments are also observed in unaffected first-degree relatives of individuals with a schizophrenia-spectrum disorder, suggesting that schizophrenia-related cognitive deficits are determined at least in part by genetics (Sitskoorn *et al.*, 2004; Snitz *et al.*, 2006). Deficits do not appear to be primarily caused by positive symptoms, as neurocognitive ability is not strongly correlated with measures of symptom severity, and deficits persist even when psychotic symptoms are in remission (Addington and Addington, 1993; Keefe and Fenton, 2007). Furthermore, treatment with antipsychotics has largely not been found to have any significant positive effect on cognitive deficits (Keefe and Fenton, 2007; Szöke *et al.*, 2008; Davidson *et al.*, 2009). Cognitive deficits appear to be relatively stable in chronic schizophrenia-spectrum disorders, with the majority of studies finding no evidence for deterioration, or possibly even improvement, in cognitive ability in established illness (Szöke *et al.*, 2008; Keefe, 2014; Heilbronner *et al.*, 2016). This suggests that the early illness stages may be a better focus for research that intends to investigate change in cognitive ability in schizophrenia-spectrum illness.

Initial studies of cognition in FEP found consistent evidence for cognitive impairment (Bilder *et al.*, 1992; Hoff *et al.*, 1992; Saykin *et al.*, 1994; Censits *et al.*, 1997). An early study by Hoff *et al.* (1992) compared first-episode schizophreniform patients, chronic individuals with a schizophrenia-spectrum disorder, and healthy controls on a range of cognitive tasks. FEP individuals were found to be impaired to the same degree as chronic patients in almost all of the cognitive domains tested, which is suggestive of a diffuse, non-specific pattern of cognitive impairment in FEP. These findings have been replicated by several subsequent studies (Addington *et al.*, 2005; Mohamed *et al.*, 2008; Mesholam-Gately *et al.*, 2009; Aas *et al.*, 2014), which have all found evidence for a generalised cognitive deficit in FEP. The cognitive domains that appear to be most affected in FEP include verbal memory, executive

functioning, general intelligence and processing speed (Mesholam-Gately *et al.*, 2009; Aas *et al.*, 2014). Additionally, a meta-analysis of cognitive deficits in high risk samples also found that impairments were present across all cognitive domains in UHR individuals (Bora *et al.*, 2014). Furthermore, UHR individuals who later transitioned to psychosis were found to exhibit a greater degree of cognitive impairment than those who did not transition (Fusar-Poli, P. Deste, G., Smieskova, R., Barlati, S., Yung, A. R., Howes, O., Stieglitz, R. D., Vita, A., McGuire, P., Borgward, 2012; Lam *et al.*, 2018; Allott *et al.*, 2019). Taken together, these findings are suggestive of widespread cognitive impairment in early psychosis.

Although cognitive deficits appear to be present in a substantial proportion of individuals with a schizophrenia-spectrum disorder, there is a large degree of heterogeneity in cognitive functioning in these individuals (Joyce *et al.*, 2005; Joyce and Roiser, 2007; Carruthers *et al.*, 2019). Early studies suggested that cognitive impairment was present in approximately 75% of individuals with a schizophrenia-spectrum disorder, compared with only 15% of the general population (Palmer *et al.*, 1997; Kremen *et al.*, 2000). These early findings are largely consistent with more recent studies showing that between 65% and 74% of individuals with schizophrenia and schizoaffective disorder can be considered cognitively impaired or cognitively deteriorated (Weinberg *et al.*, 2016; Van Rheenen *et al.*, 2017; Yasuda *et al.*, 2020). While these studies do indicate that cognitive impairment is present in most individuals with schizophrenia-spectrum disorders, they also highlight the fact that there is a proportion (~25%) of individuals for whom cognitive performance is preserved relative to healthy individuals. Initial studies found that those individuals with schizophrenia-spectrum disorders whose cognitive functioning was within normal limits, actually had significantly higher estimated premorbid ability than healthy controls, suggesting that these individuals may have experienced some level of cognitive impairment or arrest based on their expected premorbid functioning (Kremen *et al.*, 2000). Furthermore, another study found that 64% of individuals with a schizophrenia-spectrum disorder who displayed normal neurocognitive functioning had abnormal scores on at least one cognitive domain, compared to 35% of healthy controls (Allen *et al.*, 2003). Together, these findings suggest that individuals with a schizophrenia-spectrum disorder who present with normal cognitive functioning may actually have some level of impairment, either at the level of specific cognitive domains or compared to their level of premorbid functioning. However, a recent review of cognitive subgroups within schizophrenia-spectrum disorders found that three distinct subgroups may exist; one with relatively normal cognitive functioning, one

characterised by intermediate cognitive functioning or a mixed profile of cognitive impairment, and a third subgroup demonstrating severe global cognitive impairment (Carruthers *et al.*, 2019). Regardless of the subgrouping method used, it is clear that there are large variations in cognitive ability across individuals diagnosed with a schizophrenia-spectrum disorder.

1.3.2. Longitudinal course of cognition in schizophrenia-spectrum disorders

With the existence of cognitive deficits in early psychosis being generally well established, researchers are now shifting their focus to the longitudinal course of these impairments. It is currently unclear whether all areas of cognitive ability follow the same trajectory over the course of the illness, or whether different areas of cognition follow different developmental paths (Barder *et al.*, 2013). There are four developmental trajectories that cognitive abilities could potentially follow in early psychosis (Testa & Pantelis, 2009; Pantelis *et al.*, 2005; Cropley & Pantelis, 2014) (see Figure 1.2): (1) **normal development**, where performance over time is not significantly different to that of healthy controls, (2) **developmental lag**, where development occurs at a slower rate than in healthy individuals, (3) **developmental arrest**, where performance is stably impaired over time, and (4) **cognitive decline**, where performance deteriorates over time relative to healthy controls.

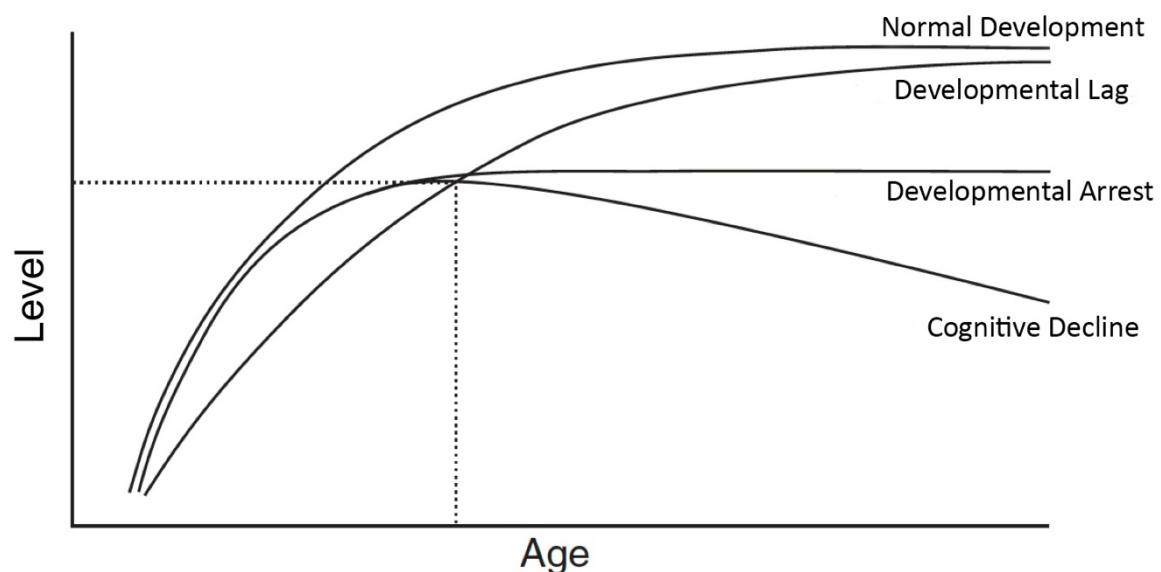


Figure 1.2. Graph depicting possible developmental trajectories of cognitive abilities in the early stages of psychotic illness. Adapted from Testa and Pantelis (2009) and Cropley and Pantelis (2014).

Currently, the dominant notion about cognition in early psychosis is that deficits are *non-progressive* following the first episode (Bozikas and Andreou, 2011; Barder *et al.*, 2013; Bora and Murray, 2013), or even from the psychosis prodrome (Bora *et al.*, 2014), which is consistent with the idea of developmental arrest. Indeed, the available evidence from longitudinal studies indicates that a number of cognitive domains, such as memory ability, language ability, executive functioning, processing speed and working memory, are impaired at psychosis onset and remain stably impaired over the course of the illness (Addington *et al.*, 2005; Bozikas and Andreou, 2011; Barder *et al.*, 2013; Zanelli *et al.*, 2019). A number of studies also provide evidence for developmental lag in the early stages of psychosis, where patients demonstrate slight improvements in their cognitive functioning over time, though they typically still show marked deficits compared to healthy controls at all time points (Albus *et al.*, 2006; Rodríguez-Sánchez *et al.*, 2008; de Mello Ayres *et al.*, 2010). Furthermore, the degree of improvement in cognitive functioning observed in the patient groups is often less than that seen in the healthy control groups (Hoff *et al.*, 2005). Thus, it would appear as though the most consistent findings to date are of stability of deficits (cognitive arrest) or slight improvements in cognitive ability in the early stages of psychosis, although there is a wide degree of variability across studies.

This variability across studies may reflect a number of methodological considerations that are likely to influence the results of longitudinal studies that focus on cognition in chronic schizophrenia-spectrum samples. In many cases, studies of established schizophrenia-spectrum patients include individuals at different illness stages, with significant variation in illness duration and number of hospitalisations. Individuals with a more chronic course of schizophrenia are also more likely to be involved with psychiatric services or be admitted to hospital or inpatient facilities. As research participants are typically recruited from such services, it is likely that samples of chronic patients will be skewed towards people who have been more severely affected by the illness. By studying patients in early illness stages, it is possible to identify the patterns of cognitive impairment that are related to the underlying neurological dysfunction of schizophrenia rather than possible illness- or treatment-related processes that may occur as the disease progresses. Furthermore, a substantial number of longitudinal studies have failed to include a healthy control comparison group, meaning that cognitive stability or change have not been considered in the context of normal cognitive development. Finally, most studies to date had follow-up periods ranging from 1 to 3 years,

which may not be long enough to capture gradual cognitive declines occurring over a longer period of time.

Recent studies, which attempted to address some of these limitations, have found evidence that some areas of cognition may actually decline in early psychosis. One area of cognitive ability that has shown some evidence of deterioration in early illness stages is episodic memory (Bozikas and Andreou, 2011; Zanelli *et al.*, 2019; Fett *et al.*, 2020). Although learning and memory is believed to be one of the most severely affected cognitive domains in the early stages of psychosis (Aas *et al.*, 2014), a handful of recent studies with long follow-up periods have found evidence for further progressive deterioration of this ability in FEP individuals (Rodríguez-Sánchez *et al.*, 2013; Zanelli *et al.*, 2019; Fett *et al.*, 2020).

Rodríguez-Sánchez *et al.* (2013) observed increasing deviation by the FEP group from healthy individuals on measures of verbal and visual memory over a 3-year follow-up period, contrasted against slight improvements in line with healthy controls in other cognitive domains. However, given the use of z-scores in this study, it is unclear whether increasing deviation in memory performance represents deterioration or failure to gain in this sample. Similarly, Zanelli *et al.* (2019) observed decreases in verbal knowledge and memory in individuals with schizophrenia over a 10-year follow-up period, whereas processing speed, executive functions, and visuospatial ability remained stably impaired. While this study again used normative scores as a comparison, making it difficult to distinguish cognitive decline from developmental lag or arrest, re-analysis of the data based on raw scores confirmed that individuals with schizophrenia were experiencing declines in memory performance rather than failure to gain relative to healthy individuals (Zanelli *et al.*, 2020).

The above studies highlight the importance of using raw score when mapping cognitive trajectories, in order to clearly decipher the slopes of these trajectories. In line with this, Fett *et al.* (2020) examined the raw cognitive scores of FEP individuals over an 18-year follow-up period and found evidence for decline in verbal and visual memory, attention and processing speed, and abstraction-executive function relative to healthy control subjects. They also found no change and improvement in verbal fluency and verbal knowledge, respectively. In all of the previous studies, cognitive deficits, including memory deficits, were present at baseline – although the level of impairment was often mild for measures of memory performance. Additionally, the baseline timepoint for the study by Fett *et al.* (2020) was two years after the onset of FEP, making it impossible to determine cognitive performance at the

time of illness onset (Mojtabai *et al.*, 2000; Reichenberg *et al.*, 2009). Taken together, the above findings suggest that both neurodevelopmental and neuroprogressive processes may be at work in individuals who have experienced a first psychotic episode, and point to episodic memory as an area of particular importance in the disorder, where there is potential to stop ongoing deterioration.

1.3.2. Memory impairment in schizophrenia-spectrum disorders

Long-term memory, in which a memory must be retained for a period ranging from several minutes to decades, is arguably one of the most central abilities necessary for everyday functioning. Though there are different types of long-term memory, one of the most comprehensively studied areas of memory functioning is episodic memory. First described by Endel Tulving (1972), episodic memory describes memories of happenings at particular places at particular times, or about “what,” “where,” and “when” (Tulving, 2002). Episodic memory is traditionally contrasted against semantic memory, which is a long-term memory store for knowledge of facts, events, ideas, and concepts that are not drawn from personal experience (Tulving, 1972). From an evolutionary perspective, episodic memory is a recently evolved area of functioning and is especially vulnerable to neuronal dysfunction (Tulving, 2002), making it of particular interest in schizophrenia-spectrum disorders. This is because schizophrenia-spectrum disorders are often characterised by abnormal brain structure and function in regions that have evolved more recently, such as the prefrontal cortex and the hippocampus (Smaers *et al.*, 2017), which show evidence of evolution beyond that seen in primates (Barger *et al.*, 2014).

Although deficits are observed across a range of cognitive domains in schizophrenia-spectrum disorders, episodic memory appears to be one of the most severely impacted areas of functioning (Heinrichs and Zakzanis, 1998; Bora *et al.*, 2009), even when accounting for factors such as duration of illness (Rushe *et al.*, 1999), antipsychotic medication (Goldberg and Weinberger, 1996), and level of psychotic symptoms (Aleman *et al.*, 1999). Thus, episodic memory impairments are considered to be a core aspect of cognitive dysfunction in individuals with schizophrenia-spectrum disorders (Guo *et al.*, 2019). In line with this, deficits in both verbal and visual memory have been shown across numerous studies to be related to, or predictive of, the functional disability that is characteristic of psychotic illnesses (Green *et al.*, 2000; Velligan *et al.*, 2000; Sota and Heinrichs, 2004; Barnett *et al.*, 2005; Prouteau *et al.*, 2005; Nuechterlein *et al.*, 2011; Juola *et al.*, 2015). In these studies, areas of

functioning that have been associated with memory ability include quality of life, return to work, personal living skills, community living, social skills, psychosocial status, and global measures of functioning, indicating that memory impairments can have far-reaching consequences for individuals with schizophrenia-spectrum disorders. Furthermore, as discussed above, recent long-term follow-up studies indicate that memory ability may deteriorate following the onset of FEP. Taken together, these findings suggest that preventing deterioration of memory ability may help to prevent or ameliorate some of the functional disability associated with the disorder. To date, however, studies of cognition in schizophrenia-spectrum disorders have focused largely on areas of functioning that are already thought to be impaired in early psychosis, with little consideration of abilities that may be preserved in FEP individuals, but deteriorate as the illness progresses.

One cognitive ability that may be preserved at illness onset but decline as the illness progresses is visual associative memory. Associative memory is a type of episodic memory that involves the forming of associations between two or more items, or between an item and its context, where these were previously unrelated (Naya, 2016). This area of functioning has been measured across a range of disorders and assessed in healthy developmental and aging studies using the paired associate learning task (PAL) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) battery (Barnett *et al.*, 2016). The PAL task was developed as a specific measure of hippocampal-dependent episodic memory, and numerous validation studies in both humans and animals have confirmed that performance on the task indexes hippocampal and prefrontal cortex integrity (Barnett *et al.*, 2016). In individuals with a schizophrenia-spectrum disorder, this task is particularly useful as a measure of episodic memory as the patterns used in the trials are not easily verbalised, meaning that scores are unlikely to be confounded by verbal impairment, which is characteristic of these disorders (Wood *et al.*, 2002; Kuperberg, 2010; Barnett *et al.*, 2016). Furthermore, a study of individuals with mild cognitive impairment also suggests that PAL performance is independent of working memory or executive abilities (Collie *et al.*, 2002). Finally, a number of different animal versions of the CANTAB PAL task have been developed, allowing for translation to non-human primates and other species (Barnett *et al.*, 2016). Thus, this task may be an ideal measure of episodic memory functioning in schizophrenia-spectrum disorders, free from interference introduced by deficits in other cognitive domains, readily translatable across species, and shown to index brain functioning in regions that are of key relevance in schizophrenia.

Cross-sectional studies have shown that, while severe deficits on the PAL task are present in individuals with established schizophrenia (Wood et al., 2002; Stip et al., 2005; Donohoe et al., 2008), this ability is preserved in FEP individuals (Wood et al., 2002; Barnett et al., 2005). Preservation of PAL ability has also been observed in individuals at UHR for psychosis, with one study showing no difference in PAL task accuracy between UHR participants and controls, although the UHR participants did have a longer response time (Fusar-Poli et al., 2010). Furthermore, a recent longitudinal study of FEP individuals with a mean treatment duration of only 21.42 days found that mean-level change occurred in a negative direction for PAL performance in the six months following psychosis onset (Haring *et al.*, 2017). Unfortunately, this study did not include a healthy control group for comparison, however these findings suggest possible deterioration of this ability immediately following psychosis onset. Studies have also demonstrated the relevance of impairments on the PAL task to functional outcomes in individuals with schizophrenia-spectrum illness. In FEP individuals, individuals who failed the PAL task were found to have higher negative symptom and psychopathology scores, as well as poorer levels of global functioning, and higher disability scores (Barnett *et al.*, 2005). In individuals with chronic schizophrenia-spectrum illness, visuospatial associative memory performance at baseline predicted improvement in daily living autonomy and social competence following participation in a rehabilitation program (Prouteau *et al.*, 2005). Given the substantial negative impact of memory impairments on everyday functioning in schizophrenia, developing a better understanding of the underlying neuropathology that contributes to these impairments may be an important first step towards identifying potential treatment targets that could lead to improved functioning in schizophrenia-spectrum disorders.

1.4. Hippocampal abnormalities and memory impairment in schizophrenia-spectrum disorders

1.4.1. Hippocampal pathology in schizophrenia-spectrum disorders

Cognitive impairments in individuals with schizophrenia are thought to be related to disturbances in the brain regions and networks that underlie these abilities. The hippocampus, a complex structure located deep within the temporal lobe (see Figure 1.3), is considered to play a critical role in these cognitive networks, particularly in relation to memory performance (Tulving, 2002; Knierim, 2015; Lisman *et al.*, 2017). Hippocampal abnormalities are one of the most robust neuropathological findings in individuals with

schizophrenia-spectrum disorders, and some researchers have suggested that hippocampal pathology may represent a biomarker for these disorders (Borgwardt *et al.*, 2012; Tregellas *et al.*, 2014; Lieberman *et al.*, 2018). While abnormalities in this region include both anatomical and functional alterations, as well as cellular and molecular pathology (Tamminga *et al.*, 2010), the current study will focus on findings related to hippocampal volumes.

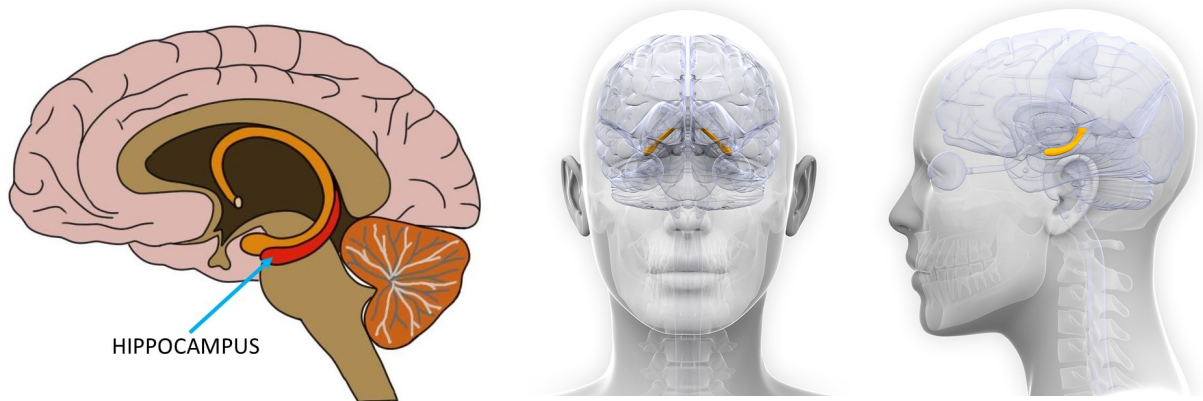


Figure 1.3. Location of the hippocampus

In individuals with chronic schizophrenia, bilateral hippocampal volume loss is well established (Velakoulis *et al.*, 1999; Wright *et al.*, 2000; Zakzanis *et al.*, 2000; Wood *et al.*, 2001; Shepherd *et al.*, 2012; van Erp *et al.*, 2016). Indeed, volume reductions are more consistently found in the hippocampus than in any other brain region in schizophrenia (Honea *et al.*, 2005; Tamminga *et al.*, 2010). A meta-analysis of over 18,000 individuals with schizophrenia-spectrum disorders estimated that hippocampal volumes in this population are approximately 6.3% smaller than those of healthy individuals (Haijma *et al.*, 2013). This is consistent with a more recent large-sample consortium study in which hippocampal volumes showed the largest volume loss out of all of the examined subcortical regions (van Erp *et al.*, 2016).

In studies that have exclusively investigated individuals in the early stages of illness, findings are less consistent. It is generally accepted that hippocampal volume loss is present in FEP individuals to the same degree as in individuals with chronic illness (Bartholomeusz *et al.*, 2016), and many studies have identified bilateral hippocampal volume reductions in this population (Copolov *et al.*, 2000; Steen *et al.*, 2006; Vita *et al.*, 2006). However, other studies have found only left (Velakoulis *et al.*, 1999, 2006; Wood *et al.*, 2010) or right (Fornito *et al.*,

2009) hemisphere hippocampal volume loss in FEP individuals, or even no volume loss prior to antipsychotic treatment (Li *et al.*, 2018). Additionally, some studies have failed to detect reduction in whole hippocampal volume in UHR samples (Velakoulis *et al.*, 2006; Walter *et al.*, 2016; Ho *et al.*, 2017). These findings, together with those of longitudinal studies in early and chronic illness, suggest an initial decline in hippocampal volumes in the earliest stages of psychotic illness, followed by relative stability following the first psychotic episode (Bartholomeusz *et al.*, 2016).

1.4.2. Hippocampal subfields in schizophrenia-spectrum disorders

The ‘hippocampus proper’ consists of several cornu ammonis subfields (CA1, CA2, CA3, CA4), each with its own distinct cellular make-up, histological characteristics, and function (Amaral and Witter, 1989). The term ‘hippocampal formation’ is typically used to describe the CA regions of the hippocampus proper, as well as the dentate gyrus and the subiculum. Together, these regions form the trisynaptic loop, which constitutes the main pathway of synaptic transmission through the hippocampus. The entorhinal cortex is the primary cortical input to the hippocampus, projecting via the perforant path onto the dentate gyrus. Dentate gyrus granule cells, in turn, pass signals on to the CA regions of the hippocampus proper. Specifically, the dentate gyrus projects onto the CA3 region via mossy fibers, and the CA3 region then sends these signals on to the CA1 through the Schaffer Collateral pathway. Finally, the CA1 projects back to the entorhinal cortex via the subiculum, completing the circuit. While connectivity through the hippocampal formation is largely unidirectional, there are a number of parallel processing circuits and feedback loops that add to the complexity of this region (Knierim, 2015). For example, while the entorhinal cortex projects primarily onto the dentate gyrus, it also connects directly to both the CA1 and CA3 subfields of the hippocampus. The CA3 region also provides feedback via mossy fibers to the dentate gyrus (DG).

Recent, high-resolution magnetic resonance imaging (MRI) studies in individuals with schizophrenia have revealed a pattern of increasing involvement of hippocampal subfields with increasing illness chronicity (Mathew *et al.*, 2014; Haukvik *et al.*, 2015; Ho *et al.*, 2016; Baglivo *et al.*, 2018). In individuals with first-episode psychosis, some studies have found volume loss to be restricted to hippocampal subfields in the left hemisphere, with one study finding reduced volumes of the left CA1, CA3, CA4, granule cell layer of the DG, and molecular layer (which, in this study, refers to a band that consists of the stratum radiatum,

lacunosum-moleculare, hippocampal sulcus, and molecular layer of the DG) (Baglivo *et al.*, 2018), and another finding reduced CA2/CA3 and CA4/DG volumes in the left hemisphere (Kawano *et al.*, 2015). It is important to note, however, that the differences observed in Baglivo *et al.*'s (2018) study were present only at a relatively liberal false discovery rate correction for multiple comparisons of $p < .10$, with no between-group differences remaining at $p < .05$, suggesting that these volume reductions were quite subtle. Another study, which combined measures across hemispheres, found volume reductions in the CA1 and DG in FEP individuals (Ota *et al.*, 2017). Conversely, volumes of the bilateral subiculum, presubiculum, hippocampal tail, alveus, fimbria, parasubiculum, and hippocampal fissure were normal relative to healthy control subjects. In individuals with chronic schizophrenia, on the other hand, hippocampal subfield volume loss has been shown to be present bilaterally, across most or all of the investigated subfields (Mathew *et al.*, 2014; Haukvik *et al.*, 2015; Ho *et al.*, 2016). The degree of volume loss across subfields varies between studies, with little consistency in terms of the subfields that are most affected in each cohort. This inconsistency may reflect a number of study-related factors, such as different illness durations and severity, MRI scan strengths, image processing pipelines and versions, the actual subfields that were investigated, the ways in which subfields were combined, and antipsychotic medication dosage.

Consistent with cross-sectional findings, a handful of longitudinal studies of hippocampal subfield volumes in schizophrenia-spectrum disorders have shown progressive volume loss across several subfields (Kawano *et al.*, 2015; Ho *et al.*, 2016; Rhindress *et al.*, 2017; Li *et al.*, 2018). In FEP individuals with little or no previous antipsychotic treatment, progressive volume loss has been observed in the CA4/DG (Kawano *et al.*, 2015; Rhindress *et al.*, 2017) and the bilateral molecular layer, DG granule cell layer, CA4, and hippocampal tails, and in the left CA1, CA3, and fimbria (Li *et al.*, 2018) following 6-weeks to 6-months of treatment. Interestingly, in the latter study, FEP individuals were found to have increased baseline subfield volumes in the molecular layer, DG granule cell layer and CA4 compared to healthy controls, and volume loss over the follow-up period normalised volumes in all of these regions except the CA4. While there are inconsistencies in terms of illness durations at baseline and length of follow-up, these findings all point to progressive abnormality in the CA4/DG in FEP individuals. Finally, a study of individuals with recent-onset schizophrenia, with less than five years illness duration, found that the volumes of all investigated subfields, which included the granule cell layer, CA4, CA3, CA1, molecular layer, hippocampal tail,

and subiculum, declined significantly over 2-7 years (average 4.5 years) in these individuals relative to healthy control subjects (Ho *et al.*, 2016). The findings of these longitudinal studies are contrary to previous longitudinal studies of whole hippocampal volume, which have tended to find stable volume deficits, with no progressive volume loss. It is possible that the ability to detect subtle longitudinal volume reductions has increased over the past several years with the increase in image resolution and improvements in segmentation pipelines. It is also possible that progressive reductions in distinct hippocampal subfield volumes have been masked by examining the hippocampus as a whole. Thus, examining hippocampal subfields individually may constitute a more informative approach to understanding hippocampal pathology in schizophrenia-spectrum disorders, and, potentially, the behavioural consequences of this pathology.

1.4.3. The hippocampus and episodic memory in schizophrenia-spectrum disorders

The critical role of the hippocampus in episodic memory functioning is well established, with decades of research demonstrating that hippocampal activation is associated with memory performance, and that hippocampal pathology results in substantial memory impairment (Vargha-khadem *et al.*, 1997; Tulving and Markowitsch, 1998; Eichenbaum and Cohen, 2001; Burgess *et al.*, 2002). One of the key functions of the hippocampus in episodic memory is in the formation of associations or relational representations between events, objects and locations (Tulving and Markowitsch, 1998). It is a key region involved in spatial or topographical memory (Eichenbaum and Cohen, 2001; Burgess *et al.*, 2002).

Given that hippocampal pathology is considered to be among the most robust of findings in schizophrenia-spectrum disorders, and the critical role of the hippocampus in memory formation and retrieval, it is perhaps unsurprising that several studies have attempted to elucidate potential relationships between hippocampal volume and memory ability in individuals with schizophrenia. In chronic schizophrenia, poorer memory performance has been associated with smaller hippocampal volumes (Gur *et al.*, 2000; Nestor *et al.*, 2007; Karnik-Henry *et al.*, 2012; Antoniadou *et al.*, 2018), suggesting that ‘bigger is better’ when it comes to relationships between hippocampal size and memory. Similar findings have been reported in FEP individuals (Hasan *et al.*, 2011; Lappin *et al.*, 2013) as well as in unaffected family members of individuals with schizophrenia (Karnik-Henry *et al.*, 2012). In healthy individuals, however, it is interesting to note that relationships between hippocampal volumes and memory performance appear to be absent or attenuated (Van Petten, 2004; Den Heijer *et*

al., 2012; Lappin *et al.*, 2013). These findings would suggest that some brain structure-cognition relationships might be mediated by disease-related neuropathology that is present only in patient groups. Furthermore, while relationships have been identified between whole hippocampal volumes and memory performance in both early and chronic schizophrenia-spectrum disorders, it is currently less clear whether these relationships are driven by whole hippocampal volumes, or whether particular regions of the hippocampus may be more critical for memory performance.

Currently there are only three known studies investigating relationships between hippocampal subfield volumes and memory ability in individuals with a schizophrenia-spectrum disorder. The first of these studies found that list-learning performance was positively associated with left CA1, CA2/CA3, subiculum, and CA4/dentate gyrus volumes (Mathew *et al.*, 2014). However, the second study failed to identify any relationships between subiculum and presubiculum volumes and a measure of delayed verbal recall in individuals with a schizophrenia-spectrum disorder, although relationships were present in individuals with bipolar disorder and in healthy controls (Haukvik *et al.*, 2015). As these authors only tested relationships between memory ability and subfield volumes in regions that differed in volume between individuals with schizophrenia and bipolar disorder (i.e. subiculum and presubiculum), it is not possible to determine whether relationships may have existed with other hippocampal subfields. Finally, a third study of individuals with FEP failed to detect relationships between hippocampal subfield volumes and a composite score of memory performance that was largely made up of verbal learning tasks (Briend *et al.*, 2020). Thus, findings to date are inconclusive, although this possibly reflects methodological differences between studies – for example, inclusion of different subfields, the use of composite measures of memory ability that may mask relationships with more specific memory measures, and differences in illness severity. Together, these findings may suggest that relationships between memory performance and hippocampal subfield volumes may exist only in the CA regions and dentate gyrus in individuals with a chronic schizophrenia-spectrum disorder, although the number of existing studies is currently too small to draw any concrete conclusions. Furthermore, it is important to note that existing studies have focused almost exclusively on verbal memory, and currently no studies have examined relationships between hippocampal subfield volumes and measures of non-verbal episodic memory.

The CANTAB PAL task, a measure of visual associative memory, is a robust measure of hippocampal integrity (Barnett *et al.*, 2016). Evidence to support the role of the hippocampus in PAL performance comes from early lesion studies, in which individuals who had undergone amygdalo-hippocampectomy, demonstrated substantial impairments on tasks of visuospatial associative memory (Owen *et al.*, 1995). Furthermore, in healthy individuals and those with Alzheimer's disease, bilateral hippocampal activation has been shown to increase alongside increasing memory load during performance on visual associative memory tasks (Gould *et al.*, 2005; De Rover *et al.*, 2011). Thus, there is evidence for the involvement of the hippocampus in visuospatial associative memory, although it is unclear whether this extends to measures of hippocampal volume and its subfields, as well as its connections to other brain regions, or whether performance on these tasks is sensitive to hippocampal pathology across different stages of psychotic illness. Given that there is possible evidence for deterioration of this ability over the course of schizophrenia-spectrum disorders (Wood *et al.*, 2002; Barnett *et al.*, 2005; Stip *et al.*, 2005; Donohoe *et al.*, 2008), and that deficits in episodic memory ability are also associated with poorer psychosocial functioning (Green *et al.*, 2000; Velligan *et al.*, 2000; Sota and Heinrichs, 2004; Barnett *et al.*, 2005; Prouteau *et al.*, 2005; Nuechterlein *et al.*, 2011; Juola *et al.*, 2015), understanding the neural mechanisms underlying these deficits may be a critical first step in ameliorating episodic memory impairments in psychotic disorders, and preventing possible deterioration of this ability as illness progresses.

1.5. Hippocampal-prefrontal dysconnectivity and memory impairment in schizophrenia-spectrum disorders

1.5.1. The dysconnection hypothesis of schizophrenia-spectrum disorders

The dysconnection hypothesis of schizophrenia posits that schizophrenia is best understood as a disorder of brain dysconnectivity, and attempts to establish links between the symptoms of the disorder and the underlying molecular and neuronal pathophysiology (Weinberger, 1993; Friston and Frith, 1995; Friston *et al.*, 2016). The brain is understood to be a distributed network of specialised regions that work synergistically to integrate and process information across a range of modalities (Mesulam, 1998). Functional integration across this network is dependent upon intact axonal and synaptic connectivity, which facilitates precise dynamic coordination of these distributed regions (Fornito and Bullmore, 2015). In schizophrenia, these networks appear to be disrupted, resulting in aberrant integration and communication of

information throughout the brain (Friston *et al.*, 2016). The dysconnection hypothesis is supported by numerous structural and functional imaging studies, which consistently demonstrate that schizophrenia-spectrum disorders are characterised by connectivity reductions relative to healthy individuals, with two key regions implicated being the prefrontal cortex and the medial temporal lobe, which is traversed by white matter tracts interconnecting the hippocampus with a number of cortical regions (Ellison-Wright and Bullmore, 2009; Pettersson-Yeo *et al.*, 2011).

1.5.2. The hippocampal-prefrontal pathway and memory

The dysconnection hypothesis of schizophrenia highlights the importance of considering distinct brain regions within their functional networks rather than in isolation. While the hippocampus is undoubtedly a critical region for memory encoding and retrieval, memory functioning is dependent on synchronised neural activity between the hippocampus and the prefrontal cortex (Li *et al.*, 2015; Sigurdsson and Duvarci, 2016). Several direct and indirect anatomical connections constitute the main efferent pathway between the hippocampus and the prefrontal cortex, and together these connections are termed the hippocampal-prefrontal pathway (Godsil *et al.*, 2013; Jin and Maren, 2015). Direct projections from the CA1 and subiculum to the prefrontal cortex terminate across the entire rostro-caudal medial prefrontal cortex (mPFC), while only sparse projections have been observed between the hippocampus and the orbitofrontal cortex (Thierry *et al.*, 2000; Jin and Maren, 2015; Li *et al.*, 2015). In addition to these monosynaptic hippocampus-mPFC projections, a number of multi-synaptic pathways link the hippocampus to the mPFC, traversing both cortical and subcortical brain regions (Godsil *et al.*, 2013; Jin and Maren, 2015; Li *et al.*, 2015). These include projections through the nucleus accumbens and ventral tegmental area, entorhinal cortex, amygdala, and thalamus, with the thalamus potentially acting as a bi-directional relay between the hippocampus and prefrontal cortex (see Figure 1.4).

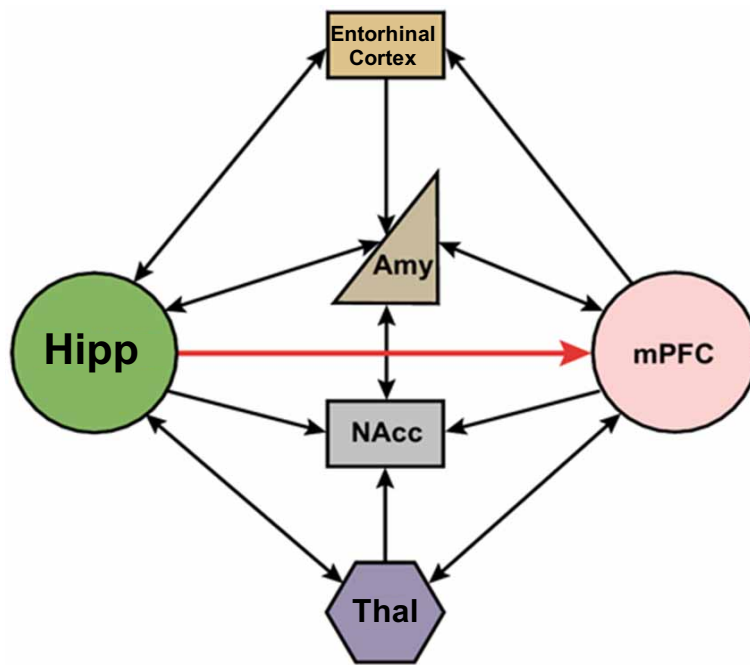


Figure 1.4. Key regions in the hippocampal-prefrontal network. Hipp, hippocampus; Amy, amygdala; NAcc, nucleus accumbens; Thal, thalamus; mPFC, medial prefrontal cortex. Adapted from Jin and Maren (2015).

Considerable evidence indicates that connectivity between the hippocampus and the prefrontal cortex is critically involved in the encoding and retrieval of episodic memory (Preston and Eichenbaum, 2013; Jin and Maren, 2015; Sigurdsson and Duvarci, 2016; Eichenbaum, 2017). Lesion studies in rats have shown that bilateral, but not unilateral, lesions of the hippocampus, the mPFC, or the pathway between them results in impairments on various memory tasks (Barker *et al.*, 2007, 2017; Chao *et al.*, 2016). Furthermore, these studies have shown that connectivity between the hippocampus and the prefrontal cortex occurs ipsilaterally. Animal studies also show that strong oscillatory activity, particularly in the theta band, between the dorsal hippocampus and the prefrontal cortex supports accurate memory performance, with a higher proportion of mPFC cells entrained to theta during encoding and retrieval when recall is accurate (Hyman *et al.*, 2005; Laubach *et al.*, 2009; Benchenane *et al.*, 2010). In humans, functional imaging studies have similarly demonstrated that, in both healthy and clinical populations, encoding and retrieval of memories is associated with coordinated activity in the hippocampus and the prefrontal cortex, particularly the mPFC (Schott *et al.*, 2013; Tompary and Davachi, 2017; Ezzyat *et al.*, 2018; Cooper and Ritchey, 2019).

Hippocampal-prefrontal dysconnectivity has been proposed to be a core feature of psychiatric disorders such as schizophrenia (Li *et al.*, 2015), and there is evidence to suggest that disruptions to this pathway may indicate vulnerability to psychosis (Godsil *et al.*, 2013). Individuals with schizophrenia have been shown to exhibit aberrant functional connectivity between the medial temporal lobe and prefrontal cortex while performing memory tasks (Meyer-Lindenberg *et al.*, 2001; Ragland *et al.*, 2004, 2015; Glahn *et al.*, 2005; Meyer-Lindenberg *et al.*, 2005; Wolf *et al.*, 2007; Rasetti *et al.*, 2011), suggesting that hippocampal-prefrontal dysconnectivity may play a role in the memory impairments that are associated with psychotic illness. Furthermore, altered hippocampal-prefrontal functional connectivity has also been observed in the first-degree relatives of individuals with schizophrenia (Rasetti *et al.*, 2011; Schneider *et al.*, 2017), and in individuals at risk of developing psychosis (Benetti *et al.*, 2009). Taken together, these findings strongly implicate abnormal hippocampal-prefrontal connectivity as a key feature of psychotic disorders.

Despite accumulating evidence for hippocampal-prefrontal dysfunction in schizophrenia-spectrum disorders, to date, in vivo imaging studies have investigated hippocampal-prefrontal connectivity exclusively by means of functional imaging studies – that is, studies that measure functional synchronisation between brain regions. However, brain connectivity (or dysconnectivity) can be measured on both a functional and a structural level. Structural connectivity in the brain is most commonly investigated using measures of white matter microstructure and connectivity, which represent different aspects of the physical connections between brain regions. As yet, no study has examined possible associations between memory impairment and white matter abnormalities in the hippocampal-prefrontal circuit.

1.5.3. White matter abnormalities in schizophrenia-spectrum disorders

White matter abnormalities in individuals with schizophrenia have been widely reported (Lee *et al.*, 2013; Di Biase *et al.*, 2017; Kelly *et al.*, 2017). One of the most commonly investigated white matter measures in schizophrenia-spectrum disorders is fractional anisotropy (FA), which is a measure of myelination, membrane permeability, and fiber density (Song *et al.*, 2002, 2003). However, more recent studies have also examined other diffusion metrics, including mean diffusivity (MD), which describes the overall diffusion of a voxel, axial diffusivity (AD), which measures parallel diffusion and is associated with axonal integrity or injury (Song *et al.*, 2003), and radial diffusivity (RD), which measures

perpendicular diffusion and is typically considered to be a measure of myelination (Song *et al.*, 2002).

To date, most diffusion imaging studies in schizophrenia-spectrum disorders have examined white matter pathology in individuals with chronic illness. These studies, which have tended to employ whole-brain voxel-wise analyses or ROI approaches, have typically identified reductions in FA in individuals with schizophrenia-spectrum disorders relative to healthy people, with the most commonly implicated fiber bundles including the superior longitudinal fasciculus, internal bundles, uncinate fasciculus, cingulum bundles, and corpus callosum (Fitzsimmons *et al.*, 2013; Wheeler *et al.*, 2014; Kelly *et al.*, 2017). Of these regions, the uncinate fasciculus and the cingulum bundle are associated with connectivity between the hippocampus and the prefrontal cortex, and may therefore be particularly relevant to episodic memory functioning (Wendelken *et al.*, 2015). A recent large-scale meta-analytic study from the Schizophrenia Working Group of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium, which combined data from 1,963 individuals with schizophrenia-spectrum disorders and 2,359 healthy controls from 29 independent studies, identified widespread white matter microstructural differences in individuals with schizophrenia that covered almost all of the examined regions of interest (Kelly *et al.*, 2017). Furthermore, while the strongest effect sizes were observed for regional FA values, the study also identified significant increases in both mean and radial diffusivity across a large number of the investigated white matter tracts, as well as significantly higher AD in the fornix. Taken together, these findings point to widespread white matter abnormalities in individuals with chronic schizophrenia-spectrum disorders.

In individuals in early illness stages, white matter findings are less consistent. A number of studies provide evidence that white matter abnormalities are present in both FEP individuals and those at risk of developing psychosis (Pérez-Iglesias *et al.*, 2010; Carletti *et al.*, 2012; Lee *et al.*, 2013; Von Hohenberg *et al.*, 2014; Alvarado-Alanis *et al.*, 2015; Cho *et al.*, 2016; Di Biase *et al.*, 2017; Rae *et al.*, 2017; Zhou *et al.*, 2017). Furthermore, studies of individuals with FEP have revealed that more severe abnormalities in white matter microstructure are present in individuals with a poorer prognosis or response to treatment (Reis Marques *et al.*, 2014; Keymer-Gausset *et al.*, 2018). There is a lack of consistency in terms of the regions that are affected in early illness stages, and a number of other studies have failed to detect white matter abnormalities in FEP individuals (Price *et al.*, 2005; Friedman *et al.*, 2008;

Peters *et al.*, 2008; Qiu *et al.*, 2009; Kong *et al.*, 2011; White *et al.*, 2011), although some of these studies are limited by small sample sizes. Despite these inconsistencies, the general consensus is that individuals in early illness stages have a milder pattern of white matter abnormalities compared to individuals with longer illness durations.

More recent studies have also employed fibre tracking (tractography) methods to examine white matter abnormalities in schizophrenia. Tractography utilises the directional information obtained in each voxel to generate visual representations of nerve tracts (Yogarajah *et al.*, 2009). As with whole brain and region of interest (ROI) studies, these studies have tended to find widespread disruptions in white matter connectivity in individuals with chronic schizophrenia (van den Heuvel *et al.*, 2010; Zalesky *et al.*, 2011; Collin *et al.*, 2014; Di Biase *et al.*, 2017; Shon *et al.*, 2018), with more subtle alterations also present in the FEP individuals and those with recent-onset illness (Price *et al.*, 2008; Zhang *et al.*, 2015a; Seitz *et al.*, 2016; Di Biase *et al.*, 2017). One advantage of fiber tracking techniques is that they allow for the interrogation of pathways implicated in specific brain networks, such as the hippocampal-prefrontal pathway. While this technique has not yet been utilised to investigate the hippocampal-prefrontal pathway in schizophrenia, it provides a promising avenue for investigating relationships between cognitive abilities and the brain networks that underlie them.

1.5.4. White matter pathology and memory impairment in schizophrenia-spectrum disorders

Although no studies have specifically investigated hippocampal-prefrontal white matter pathways, or their relationship to memory performance, in schizophrenia-spectrum disorders using fibre tracking techniques, a handful of studies have conducted ROI analyses examining relationships between microstructure of the fornix – the major output tract of the hippocampus – and memory performance. Findings of these studies are mixed, with two studies observing reduced FA and increased MD in relation to poorer memory performance in individuals with a schizophrenia-spectrum disorder (Nestor *et al.*, 2007; Takei *et al.*, 2008). A third study identified relationships between fornix microstructure and memory performance in healthy controls, which was absent in those with schizophrenia (Fitzsimmons *et al.*, 2009). Two additional studies also found that poorer memory performance was associated with reduced FA in the uncinate fasciculus in individuals with chronic schizophrenia and recent-onset (illness duration less than 4.25 years) schizophrenia-spectrum

disorders (Nestor *et al.*, 2008; Szeszko *et al.*, 2008). Thus, there is initial evidence to support the notion that memory impairment in schizophrenia-spectrum disorders is associated with white matter abnormalities, however further studies are required to tease out the specific contribution of disruptions in the hippocampal-prefrontal pathway to these impairments. Additionally, it is unclear whether these same relationships are present in FEP individuals, as the literature to date has focused primarily on individuals with chronic illness.

1.6. Rationale

Cognitive deficits are considered to be a core feature of schizophrenia-spectrum disorders, with deficits observed across a wide range of domains. Memory ability in particular, appears to be one of the most severely impacted cognitive domains in individuals with chronic illness, and recent longitudinal studies suggest that episodic memory ability may actually deteriorate over the course of the illness. This is of particular concern given that episodic memory impairments have been shown to be associated with functional disability in schizophrenia-spectrum disorders. Currently, however, studies have tended to focus on measures of verbal memory ability, which is impaired at the time of illness onset and thus thought to be a possible endophenotype for schizophrenia-spectrum disorders (Gur *et al.*, 2007). Conversely, non-verbal memory, which may be preserved or only minimally affected in early illness stages, has received substantially less attention. Tracking the trajectory of non-verbal memory abilities, such as visual associative memory ability, is vitally important, as this area of memory ability has been linked to functional outcomes in schizophrenia-spectrum disorders, including increased disability, poorer global functioning, higher negative symptoms, and impairments in daily living autonomy and social competence. While cross-sectional studies have found that visual associative memory ability is severely impaired in individuals with a chronic schizophrenia-spectrum disorder but preserved in individuals with FEP, cross-sectional studies cannot provide clear evidence of change over time. Thus, it is possible that the more severe impairments on tasks of visual associative memory observed in individuals with a chronic schizophrenia-spectrum disorder may reflect sampling bias (that is, selection of more severely ill individuals in studies of chronic schizophrenia-spectrum disorders compared to FEP studies) rather than deterioration of this ability over the course of the illness. Thus, longitudinal studies are required to determine whether discrepancies between FEP individuals and those with a chronic schizophrenia-spectrum disorder on tasks of visual associative memory are indeed due to deterioration of this ability over time.

Given that memory ability may undergo ongoing deterioration in individuals with a schizophrenia-spectrum disorder, and the fact that memory impairment is associated with more severe functional disability, the neural mechanisms underlying memory impairments in schizophrenia-spectrum disorders require further investigation. Hippocampal abnormalities represent one of the most robust neuropathological findings in individuals with schizophrenia-spectrum disorder, suggesting that further interrogation of this structure may help to further elucidate its role in memory impairment in individuals with the disorder. Identifying particular brain sub-regions or pathways that are associated with memory impairment across stages of schizophrenia-spectrum illness may help to elucidate the specific mechanisms underlying these deficits, and uncover potential treatment targets, with a goal of ameliorating these deficits, and stopping their possible progression over the course of the illness.

Although memory impairment has been linked to reductions in hippocampal volumes, it is currently unclear whether these relationships are driven by abnormalities across the entire hippocampus, or whether particular hippocampal subfields may be specifically implicated. To date, only three studies have examined relationships between hippocampal subfield volumes and memory ability in schizophrenia-spectrum disorders, with mixed results, and only one of these studies has examined relationships in FEP individuals. As the different stages of psychosis are characterised by distinct pathophysiology, it is important to examine relationships across different illness stages. With the most dynamic brain changes observed in FEP individuals in the period immediately following psychosis onset, this is a critical period in terms of investigating potential brain-behaviour relationships, such as those associated with memory ability. In individuals with chronic illness, it is possible that these relationships will have been cemented, as deterioration in memory performance and abnormalities in the regions that underlie these abilities co-occur. Furthermore, to date, studies have focused almost exclusively on measures of verbal memory, and we therefore propose to investigate brain-behaviour relationships using a visual associative memory task, which has been shown to be sensitive to underlying hippocampal pathology.

Further to this, while it is established that the hippocampus is a critical region for memory ability, numerous lesion and connectivity studies have shown that the hippocampus must work in conjunction with the prefrontal cortex for successful memory encoding and retrieval. However, to date, no studies have examined hippocampal-prefrontal white matter

connectivity in schizophrenia-spectrum disorders, and it is unclear whether white matter microstructure in this pathway is associated with memory impairment in these disorders. Furthermore, as with studies of hippocampal volume, studies investigating relationships between white matter microstructure and memory ability in schizophrenia-spectrum disorders have focused primarily on individuals with chronic illness, and have overwhelmingly utilised verbal memory tasks to index episodic memory performance.

In order to investigate these aims, three empirical studies were conducted to investigate the longitudinal trajectory of episodic memory ability following the onset of FEP, and the relationship between episodic memory performance and hippocampal subfield volumes and hippocampal-prefrontal white matter microstructure in both FEP individuals and individuals with a chronic schizophrenia-spectrum disorder.

1.7. Aims and hypotheses

This thesis was designed to address three primary questions and specific aims and hypotheses were formulated in reference to each:

1. What is the longitudinal course of episodic memory ability following a first psychotic episode?

Experiment 1 aimed to investigate the longitudinal course of visual and verbal associative memory abilities over a 5-11 year follow-up period in individuals with first-episode psychosis.

At the time that the experiment was conducted, it was hypothesised that:

- H1* Visuospatial associative memory would deteriorate over a 7-11 year follow-up period in individuals who had experienced a first psychotic episode
- H2* Verbal associative memory would remain stably impaired, or improve, following psychosis onset¹

2. Is episodic memory impairment related to hippocampal subfield volumes in FEP individuals and those with chronic schizophrenia-spectrum disorders

¹ Note that at the time the experiment was conducted, the majority of past research supported the expectation of stable impairment, however the recent publications by Fett et al 2020 and Zanelli et al 2020 suggest possible decline in this ability

Experiment 2 aimed to (i) evaluate whether FEP individuals and individuals with chronic schizophrenia-spectrum disorders differed in visuospatial associative memory performance, and hippocampal subfield volumes, in comparison with healthy controls and each other, and (ii) determine whether these patient groups exhibited differential relationships between hippocampal subfield volumes and visuospatial associative memory, compared with healthy controls and to each other.

It was hypothesised that:

- H1* Individuals with chronic schizophrenia would exhibit severe impairments in visuospatial associative memory relative to both recent-onset patients and older healthy controls, whereas recent-onset patients would perform at a similar level to younger healthy controls.
- H2* Widespread hippocampal subfield volume loss would be present in individuals with chronic schizophrenia, relative to both individuals with recent-onset psychosis and healthy controls
- H3* Stronger relationships between visuospatial associative memory and hippocampal subfield volumes would be present in patient groups relative to healthy controls

3. Is memory impairment related to white matter microstructure in the hippocampal-prefrontal pathway in early and established schizophrenia?

Experiment 3 aimed to (1) evaluate whether FEP individuals and individuals with chronic schizophrenia-spectrum disorders have abnormal white matter microstructure in the hippocampal-prefrontal pathway in comparison with healthy controls and each other, and (ii) examine relationships between white matter microstructure in the hippocampal-prefrontal pathway and visual associative memory ability in FEP individuals and individuals with chronic schizophrenia-spectrum disorder, using both region-of-interest and tractography approaches.

It was hypothesised that:

- H1* Individuals with chronic schizophrenia would exhibit severe abnormalities in white matter microstructure in relation to healthy controls, whereas FEP individuals would exhibit milder abnormalities compared to healthy controls.
- H2* Visuospatial associative memory performance would be associated with reduced white matter integrity in key tracts, including the dorsal and ventral cingulum bundle, the uncinate fasciculus, and the fornix, which are involved in hippocampal connectivity.

H3 Visuospatial associative memory performance would be associated with abnormal white matter microstructure between the hippocampus and key regions involved in the hippocampal-prefrontal pathway, including the thalamus, amygdala, nucleus accumbens, and medial prefrontal cortex.

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CHAPTER 2: General Methodology

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2.1. Assessment of episodic memory

Episodic learning and memory was assessed across all samples using the The Cambridge Neuropsychological Test Automated Battery (CANTAB) Paired Associates Learning (PAL) task (Cambridge Cognition, 2016). This task measures the ability to remember object-location associations, and is considered to be a measure of medial temporal lobe functioning (Barnett et al., 2016). In the early stages of the task, six white boxes are spaced evenly on the screen, and opened up in a random order to reveal a coloured pattern inside (see Figure 2.1 A). After all the boxes have been opened, each pattern is then shown in the centre of the screen and the participant must touch the box where that pattern was located (see Figure 2.1 B). If the participant makes an error, the patterns are re-presented to remind the participant of their locations. In the first trial, only one box contains a coloured pattern, and the number of patterns increases in subsequent trials. The final stage of the task requires participants to remember the locations of eight different patterns in eight boxes.

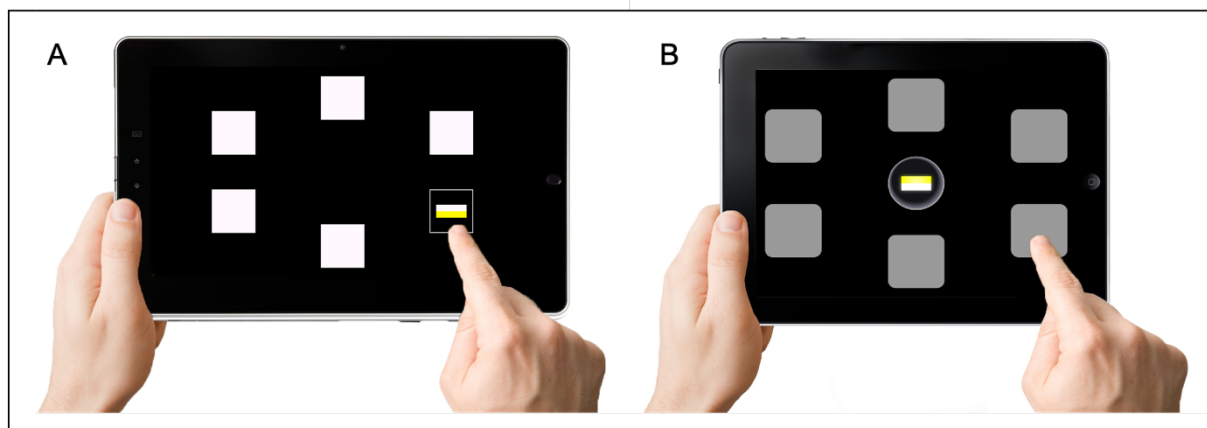


Figure 2.1. Visualisation of the CANTAB PAL task. In image A, the location of coloured pattern is revealed. In image B, the participant is required to touch the box where they recall seeing the coloured pattern.

2.2. Hippocampal segmentation

2.2.1. Image acquisition

Magnetic resonance images were acquired on the same day as cognitive testing on a Siemens Avanto 3 T Magnetom TIM Trio scanner at the Murdoch Children's Research Institute,

Royal Children's Hospital, Parkville, VIC, Australia. T1-weighted images were acquired using an optimized Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. The sequence parameters were: 176 sagittal slices of 1 mm thickness without gap, field of view (FOV) = $250 \times 250 \text{ mm}^2$, repetition time (TR) = 1980 ms, echo time (TE) = 4.3 ms, flip angle = 15° , using an acquisition matrix of 256×256 resulting in a final reconstructed voxel resolution of $0.98 \times 0.98 \times 1.0 \text{ mm}^3$.

2.2.2 Image processing

Data were pre-processed using the bpipe library (<https://github.com/CobraLab/minc-bpipe-library>). This pipeline performs N4 bias field correction, removes any non-brain tissue, transforms images to MNI space using bestlinreg, and creates a binarised brain mask. Bpipe provides output in two spaces – native space and MNI space – and the native space output was used for hippocampal segmentation.

Fully-automated segmentation of the hippocampus was carried out using the MAGeT Brain algorithm (Chakravarty et al., 2013; Pipitone et al., 2014: <http://github.com/CobraLab/MAGeTbrain>). This modified multi-atlas segmentation technique is designed to use a limited number of high-quality manually segmented atlases of the hippocampal subfields as input (Pipitone et al., 2014). These atlases include definitions for the right and left CA1, CA2CA3, CA4/dentate gyrus (CA4DG), strata radiatum/lacunosum/moleculare (SRLM), and subiculum (see Figure 2.2). Atlas segmentations are propagated to a template library and then to subjects using nonlinear registration (Avants et al., 2008), and a subset of the population under study is used as the template library through which the final segmentation is bootstrapped. Each subject in the template library is segmented through nonlinear atlas-to-template registration followed by label propagation, yielding 5 unique definitions of the hippocampus for each of the templates. In the current study, 21 templates, consisting of ten controls and eleven patients, were selected based on age and gender to ensure a representative template set. This resulted in 105 candidate labels for each subject, and labels were then fused using a majority vote to complete the segmentation process. As the dentate gyrus and subiculum are included within the MAGeT Brain algorithm, the term “hippocampus” used throughout this manuscript encompasses the hippocampal formation.

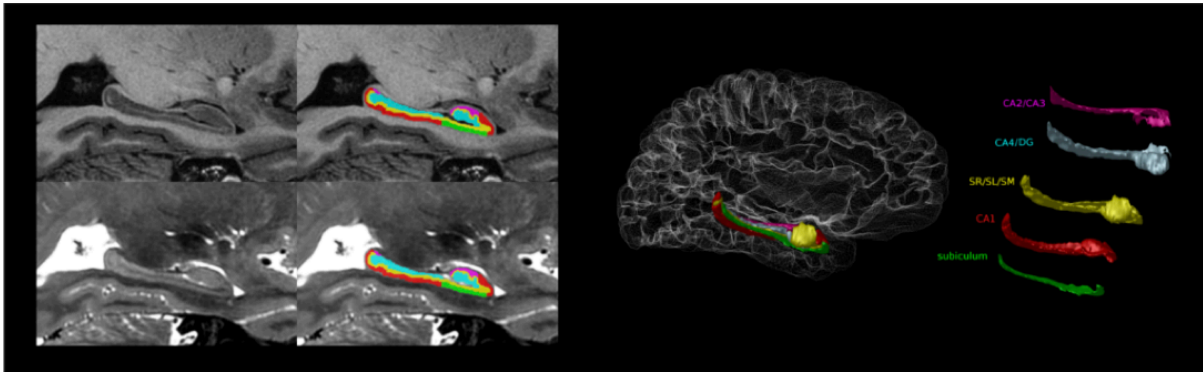


Figure 2.2. Visualisation of hippocampal subfield segmentation in a single subject, with each subfield represented by a different colour. Reprinted with permission from Winterburn et al., 2013.

Quality assurance for each scan was carried out at three time points. First, unprocessed minc files were visually inspected for abnormalities and to ensure image quality and orientation. Second, following data pre-processing with bpipe, scans were inspected to ensure successful registration to MNI space and inhomogeneity correction. Finally, following processing with MAGeT Brain, each participant's hippocampal subfield segmentation was visually inspected to ensure segmentation quality using a three point system: 0 = fail; 0.5 = good pass; 1 = excellent pass.

2.3. White matter microstructure

2.3.5. *Quantification of white matter microstructure*

Diffusion-weighted MRI measures water molecule displacement inside and around brain tissue (Fornito et al., 2012; Soares et al., 2013). The basic concept underlying diffusion tensor imaging (DTI) is that the diffusion characteristics of water molecules vary depending on the type of tissue being examined (white matter, grey matter, cerebrospinal fluid, etc.) and the integrity and architecture of that tissue (Beaulieu, 2002; Chenevert et al., 1990; Soares et al., 2013), with water diffusing more freely along coherent fibre bundles than across them (Johansen-Berg and Rushworth, 2009).

When diffusion weighted images (DWI) are acquired, multiple brain images are acquired, and, for each image, a signal is sensitised to diffusion along different directions (Johansen-Berg and Rushworth, 2009). For each brain voxel it is therefore possible to build up a three-dimensional pixel, and mathematical models can be used to estimate diffusion within the voxel. The most commonly used model is the tensor model, where an ellipsoid is fitted to each voxel to characterise its diffusion properties (Mori and Zhang, 2006). Each ellipsoid, or

tensor, is estimated using measurements across six different axes: three orthogonal eigenvectors, which define the fiber tract orientation, and their three corresponding eigenvalues, or lengths (Johansen-Berg and Rushworth, 2009; Mori and Zhang, 2006). If diffusion is constrained (anisotropic), the ellipsoid will be cigar-shaped, and if it is unconstrained (isotropic), the ellipsoid will be round (see Figure 2.3, adapted from Johansen-Berg and Rushworth (2009)). Using the tensor model, the degree of anisotropy within a voxel is characterised by fractional anisotropy (FA), which is calculated from the three eigenvalues and is the most commonly utilised measure of white matter microstructure. FA ranges from zero, which represents full isotropy, to one, which represents full anisotropy (O'Donnell and Westin, 2011). While FA measures how far a voxel is from a sphere, it is also possible to measure the extent to which diffusion occurs parallel- and perpendicular to the primary axis of diffusion. Namely, axial diffusivity, which is derived from the largest eigenvalue and measures the diffusion rate along the principal axis, and radial diffusivity, which is derived from the second and third eigenvalues, and measures diffusion perpendicular to the primary axis (Soares et al., 2013). Mean diffusivity, which is calculated by taking the mean of the three eigenvalues, is also a commonly used measure of white matter microstructure. However, examining axial and radial diffusivity separately may be more useful for identifying the type of pathology underlying white matter abnormalities in certain diseases. That is, axial diffusivity is typically thought to index axonal degeneration, whereas radial diffusivity is considered to be a measure of myelination (Alexander et al., 2007; Song et al., 2002, 2003).

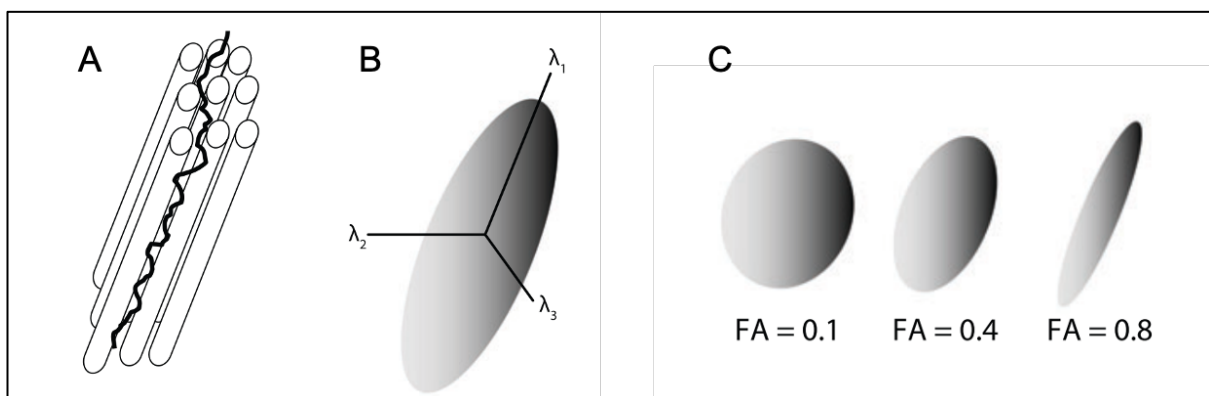


Figure 2.3. The diffusion tensor model. (A) Illustration of diffusion of a water molecule (black line) within a fiber bundle (B) Water diffusion at each voxel is modelled using a tensor, characterized by its three principal eigenvectors and their associated eigenvalues (λ_1 , λ_2 , λ_3) (C) Eigenvalues are used to calculate fractional anisotropy (FA), which ranges

between zero (isotropic) and one (anisotropic). Adapted from (Johansen-Berg and Rushworth, 2009)

2.3.2. Processing and analysis of diffusion data

Processing and analysis of diffusion data can loosely be categorised into three modalities: (1) whole-brain, (2) region of interest (ROI), and (3) tractography. The most common whole-brain approach is tract-based spatial statistics (TBSS; Smith et al., 2006), which was designed to overcome limitations associated with aligning FA from multiple subjects to a standardised template for analysis. TBSS uses non-linear registration to align each subject's FA map into 1x1x1mm MNI152 space, and then projects this registered FA map onto a mean FA skeleton, which is created by averaging FA across all subjects in a study (Smith et al., 2006). The projection of each individual's FA onto the mean FA skeleton occurs by searching perpendicular to the mean skeleton structure for the maximum value in the subject's FA image, and then filling the skeleton with FA values from the nearest relevant tract centre. To avoid partial volume effects, whereby grey matter or cerebrospinal fluid (CSF) are contributing to the diffusion signal, individual FA maps are thresholded so that only voxels with FA greater than 0.2 are included. Voxel-wise analyses can then be carried out to examine group differences or relationships with variables of interest across the whole brain.

In contrast to whole-brain approaches, ROI approaches only investigate group differences or relationships in specific white matter tracts, typically chosen based on a priori hypotheses. Masks derived from well-established white matter atlases, such as the John Hopkins University (JHU) white matter tractography atlas (Wakana et al., 2004), are typically applied to either preprocessed diffusion tensor data, or to skeletonised output from TBSS. ROI approaches as they allow researchers to limit analyses to white matter tracts that are thought to be relevant to their particular research question, without having to correct for multiple comparisons across the entire brain. This is particularly relevant for cognition studies, where relevant brain networks are typically restricted to frontotemporal or frontoparietal pathways (Bressler and Menon, 2010). However, it is still possible that circumscribed pathology affecting only a small portion of a larger white matter tract could still be overlooked, as ROI approaches average over entire tracts.

Finally, tractography approaches utilise the anisotropic diffusion of water to determine intervoxel connectivity (Mukherjee et al., 2008), and are the most direct approaches to

measure white matter connectivity using diffusion weighted brain images. Fiber tracking algorithms are divided into two primary methods: deterministic and probabilistic tractography. In deterministic methods, fiber trajectories follow the primary axis of diffusion from voxel to voxel, changing direction to match the primary diffusion direction of the next voxel (Mukherjee et al., 2008). Deterministic methods are therefore said to generate one white matter fiber from each seed voxel (Soares et al., 2013). The specificity of deterministic tractography is high, meaning that it accurately distinguishes white matter tracts, however these models assume that each voxel has only a single fiber orientation, and therefore cannot account for crossing fibers or other factors that might cause uncertainty in the orientation of the diffusion ellipsoid (Jones, 2010; Mukherjee et al., 2008). Thus, these approaches may result in false negatives, whereby fibers with more complex fiber orientation metrics are excluded. Furthermore, deterministic approaches will track an erroneous pathway with the same level of confidence as an incorrect one (Jones, 2010). Probabilistic approaches attempt to overcome these limitations by estimating connection probability at each voxel, resulting in a distribution of estimates of fiber orientation from which the next propagation direction can be chosen (Jones, 2010). Such an approach is better able to account for uncertainty in the orientation of the diffusion ellipsoid caused by factors such as crossing, twisting, bending, and kissing fibers, as well as individual-level factors such as movement, imaging artifacts, and noise (Mukherjee et al., 2008). One limitation of probabilistic approaches, however, is that the more lenient inclusion criteria may lead to false-positives, resulting in densely connected tractography maps with reduced specificity when compared to deterministic approaches (Zalesky et al., 2016). Two main approaches can be taken to mitigate the possibility of false-positives. The first is to threshold generated tracts so that voxels with a low probability of connection are excluded (van Wijk et al., 2010). The second is to use the generated probability maps to calculate weighted mean values of white matter microstructure, whereby voxels that have a higher probability of connection contribute more strongly to the mean.

2.3.1. Image acquisition

Sixty diffusion-weighted volumes and 10 diffusion-unweighted (b0) volumes were obtained with an echo planar imaging sequence on a Siemens Avanto 3 T Magnetom TIM Trio scanner at the Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, VIC, Australia. Acquisition parameters were as follows: b-value = 3000s/mm², slice

thickness = 2mm, image matrix = 104 x 104, in plane voxel resolution = 2 x 2 mm, field of view = 208 x 208, repetition time = 7750 ms, echo time = 112 ms, flip angle = 90°.

2.3.2. Image Processing

Diffusion-weighted imaging (DWI) data were pre-processed and registered to normalized stereotaxic space with the FMRIB Software Library (FSL; Jenkinson *et al.*, 2012). Pre-processing involved visual inspection for artifacts, during which six scans were removed from the analysis (1 control and 5 patients) due to poor image quality (cerebellar cropping and movement artifact) and another scan removed (1 patient), due to an incomplete imaging sequence. The remaining scans (sample population described in Table 1) underwent correction for motion and gradient-induced currents using affine registration to the first b0 image, and computation of FA, RD, and axial diffusivity (AD) volumes by fitting a tensor to the raw data using the FMRIB diffusion toolkit (FDT). Tract-based spatial statistics (TBSS) analysis of the diffusion-weighted data was then performed in the FSL software package according to the standard procedure (Smith *et al.*, 2006). In brief, each subject's FA maps were first co-registered using non-linear registration (Andersson *et al.*, 2007) to 1x1x1mm standard space, resulting in a standard space version of each individual FA image. Next, a study-specific thinned mean FA skeleton was generated to represent the centre of all white matter FA voxels common to the group. This mean FA skeleton was thresholded at 0.2 to ensure that grey matter and cerebrospinal fluid were excluded from analyses. Voxel values of each subject's FA map were projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton.

2.3.3. ROI Analysis

Mean white matter measurements of FA, RD and AD were extracted from ROIs using a number of masks applied to the skeletonised TBSS data. A bilateral fornix mask, obtained using a novel template developed by Brown *et al.* (Brown *et al.*, 2017), was used due to difficulties separating the structure over the midline of the brain. An additional three ROIs in each hemisphere – the dorsal and ventral cingulum bundles, and the uncinate fasciculus, were selected from the John Hopkins University (JHU) white matter tractography atlas (Hua *et al.*, 2008; Mori *et al.*, 2005; Wakana *et al.*, 2004). ROI masks were restricted to the mean FA skeleton mask.

2.3.4. Tractography

Probabilistic tractography from the seed region (hippocampus) to the target regions (mPFC, thalamus, nucleus accumbens, amygdala) was performed using FSL's ProbtrackX program (Behrens et al., 2003, 2007). The hippocampus was extracted using MAGeT Brain software (Chakravarty et al., 2013; Pipitone et al., 2014: <http://github.com/CobraLab/MAGeTbrain>), as described previously (Wannan et al., 2018), and target regions were extracted using FSL's Harvard-Oxford probabilistic cortical and subcortical atlases, thresholded at 25%. Seed and target regions were non-linearly registered to each participant in the current study using the method described above. As hippocampal-prefrontal connections are largely ipsilateral, tractography was performed separately for each hemisphere, and the contralateral hemisphere was excluded from analyses using a mask. Five thousand samples were initiated from each voxel in the seed region, and we used a step-length of 0.5mm, and fiber threshold of 0.01. Resulting pathways were normalised by dividing the number of streamlines passing through each voxel by the total number of generated streamlines (i.e., the waytotal value in FSL). This approach helps to ensure that results are not adversely impacted by differing mask sizes, tract sizes, or inclusion of voxels with a low probability of truly falling within a generated tract. The normalised pathways were then used to extract weighted mean FA, RD, and AD values, whereby voxels that had a higher probability of connection contributed more heavily towards the calculated mean value.

Tractography successfully tracked pathways between the hippocampus and the amygdala, nucleus accumbens, and thalamus in both hemispheres. However, tractography between the hippocampus and mPFC did not produce reliable tracts, possibly reflecting the sparse physical connections between these two regions, and these analyses were therefore excluded from further interrogation.

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CHAPTER 3:

Deterioration of visuospatial associative memory following a first psychotic episode: a long-term follow-up study

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Deterioration of Visuospatial Associative Memory Following a First Psychotic Episode: A Long-term Follow-up Study

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Abstract

Background. Cognitive deficits are a core feature of schizophrenia, and impairments in most domains are thought to be stable over the course of the illness. However, cross-sectional evidence indicates that some areas of cognition, such as visuospatial associative memory, may be preserved in the early stages of psychosis, but become impaired in later established illness stages. This longitudinal study investigated change in visuospatial and verbal associative memory following psychosis onset.

Methods. 95 first-episode psychosis (FEP) patients and 63 healthy controls (HC) were assessed on neuropsychological tests at baseline, with 38 FEP and 22 HCs returning for follow-up assessment at 5-11 years. Visuospatial associative memory was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) Visuospatial Paired-Associate Learning (PAL) task, and verbal associative memory was assessed using Verbal Paired Associates (VPA) subtest of the Wechsler Memory Scale - Revised.

Results. Visuospatial and verbal associative memory at baseline did not differ significantly between FEP patients and healthy controls. However, over follow-up, visuospatial associative memory deteriorated significantly for the FEP group, relative to healthy individuals. Conversely, verbal associative memory improved to a similar degree observed in healthy controls. In the FEP cohort, visuospatial (but not verbal) associative memory ability at baseline was associated with functional outcome at follow-up.

Conclusions. Areas of cognition that develop prior to psychosis onset, such as visuospatial and verbal associative memory, may be preserved early in the illness. Later deterioration in visuospatial memory ability may relate to progressive structural and functional brain abnormalities that occur following psychosis onset.

Introduction

Cognitive deficits are considered to be a core feature of the schizophrenia-spectrum, with impairments present in both first-episode psychosis (FEP) patients, and in individuals with established illness (Aas et al. 2014; Bora et al. 2009). Although deficits are observed across virtually all cognitive domains, the greatest levels of impairment are seen in attention, executive function, verbal fluency, and verbal learning and memory (Fatouros-Bergman et al. 2014; Bora et al. 2009; Aas et al. 2014).

Currently, deficits in cognition in schizophrenia are thought to be present at the time of illness onset and to remain stable over its course (Bora & Murray 2013). This is consistent with the prevailing neurodevelopmental hypothesis, which posits that abnormal brain development leads to arrested maturation of cognitive abilities in individuals who go on to develop schizophrenia (Weinberger 1987) (Murray & Lewis 1987). Indeed, the evidence from longitudinal studies shows that the cognitive performance of individuals at ultra-high risk (UHR) of developing psychosis and FEP patients improves over time (Bora & Murray 2013). These findings indicate that cognitive deficits are present prior to the onset of prodromal symptoms, with no evidence for a decline in functioning as the illness progresses.

Cross-sectional studies on the other hand, provide evidence for cognitive *deterioration* following psychosis onset (Napal et al. 2012), at least in some areas of cognitive functioning. These studies, which typically compare cognitive functioning in early illness stages with that of chronic schizophrenia patients, tend to report more severe cognitive impairment in individuals with chronic or multi-episode schizophrenia (Keefe 2014; Napal et al. 2012; Braw et al. 2008). A recent review of cognitive ability at different illness stages revealed that individuals at UHR of developing psychosis demonstrated only mild cognitive impairments, with performance approximately 0.5 standard deviations below that of healthy individuals (Keefe 2014). Recent onset patients, on the other hand, demonstrated cognitive performance approximately 1.5 standard deviations below that of healthy comparison subjects. However, the largest deficits were observed in individuals with chronic schizophrenia, whose performance sat around 2.5 standard deviations below that of healthy individuals. Taken together, these findings suggest that cognition may deteriorate as the severity of illness

increases, or that poor clinical outcome is associated with poor cognitive performance (Bodnar et al. 2008; Carlsson et al. 2006; Leeson et al. 2009).

Visuospatial associative memory is one area of cognition that has been found to be more impaired in individuals with established schizophrenia than in FEP patients (Wood et al. 2002; Barnett et al. 2005; Stip et al. 2005; Donohoe et al. 2008). A previous cross-sectional study found that performance on the Cambridge Neuropsychological Test Automated Battery (CANTAB) paired-associates learning (PAL) task was preserved in FEP patients, who performed at a level similar to that of healthy controls (Wood et al. 2002). Conversely, chronic patients demonstrated impaired PAL performance when compared to both healthy controls and to FEP patients. This discrepancy in cognitive performance between cohorts could indicate a deteriorating course – however, it could also be that poorer PAL performance in FEP is predictive of chronic illness outcome. To date, PAL performance has not been measured longitudinally over time in first-episode schizophrenia patients. Therefore, this question of a ‘deteriorating’ visuospatial memory course versus the prognostic value of low PAL ability remains to be directly assessed.

Here we report the results of the first longitudinal study of visuospatial associative memory performance in FEP patients, followed up over five to ten years. Our aim was to investigate the longitudinal course of visuospatial associative memory ability following psychosis onset, and to compare this with the course of verbal associative memory ability over the same period. Based on previous cross-sectional findings, we hypothesised that visuospatial associative memory would deteriorate over the follow-up period for the FEP patients, whereas the performance of the healthy controls would remain stable. Verbal associative memory was expected to remain stable, or to improve, in both FEP patients and healthy controls over the follow-up period.

Method

Participants and Clinical Assessment

Table 1 presents the demographic and clinical characteristics of the sample. At baseline, 95 individuals experiencing a first episode psychosis (FEP) were recruited from Orygen Youth

Health's Early Psychosis Prevention and Intervention Centre (EIC), Melbourne, Australia between 1993-2001. Diagnoses included schizophrenia ($N = 19$), schizophreniform disorder ($N = 45$), schizoaffective disorder ($N = 17$), delusional disorder ($N = 2$), brief psychotic disorder ($N = 4$), psychotic disorder not otherwise specified ($N = 6$), and substance-induced psychosis ($N = 2$). FEP-specific inclusion criteria were; (1) current DSM-III(American Psychiatric Association 1987) Axis I diagnosis of a psychotic disorder; and (2) less than 6 months of neuroleptic treatment. The current study also excluded FEP patients with a primary mood diagnosis (bipolar disorder and depression). The Royal Park Multidiagnostic Instrument for Psychosis (RPMIP)(Mcgorry et al. 1990) and the Structured Diagnostic Interview for DSM-III (SCID-I/P)(First et al. 2002) were used to determine diagnosis. Further information about the methodology has been described previously (Henry et al. 2007). Healthy control (HC) participants ($N = 63$) were recruited from the same catchment area as patients. HCs with a history of psychiatric illness were excluded. Exclusion criteria for FEP and HC included: significant head injury and/or loss of consciousness for > 1 minute; preferred language other than English; known history of learning disability; estimated premorbid IQ < 70 based on the National Adult Reading Test (NART)(Nelson & Willison 1991); DSM diagnosis of substance abuse or dependence; neurological disease; baseline age > 45 . All participants provided informed consent and had adequate English comprehension.

Follow-up assessments were carried out between 1998 and 2005. Thirty-eight FEP and 22 HCs completed follow-up cognitive assessment, although a number of participants did not complete all cognitive tasks (see Table 2). For the FEP patients, level of functioning at follow-up was measured using the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al. 1992).

Cognitive measures

Estimated premorbid IQ was measured with the NART(Nelson & Willison 1991). NART scores were converted to Wechsler Adult Intelligence Scale-Revised intelligence quotient (WAIS-R IQ)(Wechsler 1981) scores. Four subtests of the WAIS-R were used to obtain an estimate of current full scale IQ.

Visuospatial associative memory was assessed using the Visuospatial Paired-Associate Learning (PAL) Task from the CANTAB (Cambridge Cognition 2016). This task uses cued recall of a series of patterns at different spatial locations. In the early stages of the task, six white boxes are spaced evenly on the screen, and opened up in a random order to reveal a coloured pattern inside. In the first trial, only one box contains a coloured pattern. Once all of the boxes have opened, the pattern is displayed in the centre of the screen and the participant is required to touch the box in which it was located. The number of patterns increases in subsequent trials, and the final stage of the task requires participants to remember the locations of 8 different patterns. The number of errors on the final stage of the task (8 shapes) was the variable of interest for the current study. Participants who did not reach the 8 shape stage of the task were given an adjusted score of 70 as described in the CANTAB administration guide (Cambridge Cognition 2012). This adjustment is calculated using the following formula:

$$\left(\text{Number of patterns not attempted (8)} - \frac{\text{Number of boxes (8)}}{\text{Number of patterns (8)}} \right) \times \text{Total number of patterns (10)}$$

Basic visual recognition was measured with the Pattern Recognition (PR) task from the CANTAB (Cambridge Cognition 2016). In a white box in the centre of the screen, a series of 12 patterns were displayed one by one. Patterns were designed so that they cannot be easily verbalised. In the recognition phase, the participant is required to choose between a novel pattern and a pattern that they have already seen. Patterns are presented in reverse order in the recognition phase. This sub-test is then repeated with a second set of patterns, and participants are given a score out of 24.

Verbal associative memory was assessed using the semantically-unrelated (difficult) pairs from the Wechsler Memory Scale-Revised (WMS-R) Verbal Paired Associates (VPA) task (Wechsler 1987). In this task, participants were first read a list of 4 word pairs. The examiner then read the first word of each pair, and the participant is asked to provide the corresponding word. Three trials were completed.

Data Analysis

Group differences between FEP patients and healthy controls on demographic measures were examined using chi-square tests for categorical data, and independent groups t-tests for

continuous variables.

Due to the fact that PAL errors are recorded as a count variable, and data were overdispersed (the variance was substantially greater than the mean), generalised estimating equations (GEE) negative binomial regression was determined to be the most appropriate method for examining change in PAL scores over time. Stepwise backward selection criteria were employed to determine the final model: all independent variables (IV) were initially entered into the model and then variables with a p value > 0.05 were removed. Group and time (time 1, time 2), as well as the group $\times$ time interaction, were included as IVs in each model. Initial covariates included age, IQ, years of education, sex, length of follow-up, and PR scores. PR was included as a covariate in the analysis of PAL performance as it has been found to predict performance on the PAL task in previous studies (Wood et al. 2002). GEE allows for missing data at each time-point, however data must be missing completely at random. As data-screening analyses confirmed that missing data at follow-up were not related to any variables of interest (including: age, sex, diagnosis, baseline cognition scores [PAL errors, verbal memory scores, IQ, estimated premorbid IQ], or years of education), data was deemed missing completely at random, and participants with missing data were thus included in the analysis.

A generalised linear mixed model was used to analyse change in VPA performance over time. This model allows the slope or intercept to vary across participants as a random effect (Laird & Ware 1982). Again, stepwise backward selection criteria were employed to determine the final model. In the initial model, VPA scores were included as the dependent variable, and group, time (time 1, time 2), group $\times$ time, age, IQ, and years of education were included as fixed effects. Our analyses included all available data collected for each participant at each time-point.

Relationships between neuropsychological test scores (PAL and VPA) and social and occupational functioning at follow-up were analysed using Spearman's rank order correlations.

Results

Demographics

FEP patients had a significantly shorter follow-up interval than HCs, and a significantly lower age at follow-up (see Table 1). HCs also completed more years of education, and had higher estimated premorbid IQ scores than FEP patients. Neuropsychological assessment scores at baseline and follow-up are displayed in Table 2.

Table 1. *Demographics*

	FEP	HC	<i>t/χ²</i>
Baseline			
<i>n</i>	95	63	
Gender (M/F)	67/28	42/21	$\chi^2=0.26$, NS
Age	21.59 (3.42)	22.91 (5.77)	$t = -1.64$, NS
Handedness (right)	81	58	$\chi^2=1.66$, NS
Predicted WAIS-R IQ	96.00 (10.01)	102.13 (10.65)	$t = 3.38^{**}$
Age of illness onset	21.53 (3.65)		
Prodrome length (months)	9.35 (12.60)	-	
DOI baseline (years)	0.31 (0.49)	-	
Medication dose (CPZ equivalent) (mg)	192.40 (298.11)	-	
Follow-up			
<i>n</i>	38	22	
Age	28.67 (3.96)	32.64 (6.16)	$t = 2.76^*$
Length of follow-up (years)	6.93 (1.43)	8.49 (1.82)	$t = 3.72^{**}$
Follow-up range (years)	5.26-10.99	5.25-11.64	
Years of education	12.97 (1.98)	16.39 (2.68)	$t = 5.67^{**}$
DOI at follow-up (years)	7.42 (1.46)	-	
SOFAS	67.35 (15.76)	-	

* $p < .05$; ** $p < .01$, NS = Not significant

Abbreviations: FEP, First-episode Psychosis; HC, Healthy Control; DOI, Duration of Illness; CPZ, chlorpromazine; SOFAS, Social and Occupational Functioning Assessment Scale

Visuospatial associative memory

Table 3 displays the results of the generalised estimating equation model for PAL performance. IQ, sex, and PR performance were included as covariates in the final model. IQ and PR scores were negatively correlated with PAL performance, with lower scores associated with more errors on the PAL task. There was also a main effect of sex, with males making more errors than females. A significant group $\times$ time interaction was also observed (Wald $\chi^2(1)=6.02$, $p=.014$): At baseline, there was no difference between FEP individuals and

HCs in terms of PAL errors, however the HC group demonstrated slight improvement on the PAL task over time, whereas performance of the FEP group deteriorated from baseline to follow-up (see Figure 1A).

Verbal Associative Memory

Table 4 displays the generalised linear mixed model for VPA performance. IQ was included as a covariate in the final model as IQ scores were positively related to VPA scores. A main effect of time was also observed, with both groups' performance improving over the follow-up period. There was no main effect of group, and no group $\times$ time interaction.

Table 2. *Cognitive performance at baseline and follow-up*

		FEP		HC	
Task		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
PAL errors	Baseline	53	8.58 (11.79)	33	4.97 (7.95)
	Follow-up	28	14.82 (17.44)	16	3.19 (5.08)
PR	Baseline	59	19.32 (3.06)	32	21.97 (2.21)
	Follow-up	28	20.39 (3.41)	16	22.44 (2.03)
VPA	Baseline	94	5.78 (3.33)	62	7.66 (2.96)
	Follow-up	36	7.50 (2.85)	21	9.62 (1.77)
IQ	Baseline	89	89.08 (11.64)	59	107.76 (11.31)
	Follow-up	34	92.32 (8.40)	20	107.75 (10.02)

Abbreviations: FEP, First-episode Psychosis; HC, Healthy Control; PAL, Paired Associates Learning; PR, Pattern Recognition; VPA, Verbal Paired-Associates

Table 3. *GEE Negative binomial regression model for PAL performance*

	Odds ratio (95%CI)	<i>p</i>
IQ	0.99 (0.97-1.00)	.050
PR	0.83 (0.78-0.89)	<.001
Sex	1.76 (1.13-2.75)	.012
FEP Group	1.10 (0.63-1.92)	.730
Time (follow-up)	0.64 (0.32-1.27)	.201
FEP Group x Time	2.76 (1.23-6.23)	.014

Abbreviations: FEP, First-episode Psychosis; HC, Healthy Control; PR, Pattern Recognition; PAL, Paired Associates Learning

Correlations with Functioning

For patients, number of errors on the PAL task at baseline was significantly negatively correlated with level of functioning at follow-up, $r_s(26) = -0.38$ $p = .045$. There was no correlation between baseline VPA performance and SOFAS scores at follow-up. Number of PAL errors at follow-up was significantly negatively correlated with SOFAS scores at follow-up, $r_s(34) = -0.37$ $p = .027$. VPA scores at follow-up were also significantly correlated with SOFAS scores at follow-up, $r_s(35) = -0.41$ $p = .012$.

Table 4. Generalized linear mixed model for VPA performance

	Coefficient (95%CI)	<i>p</i>
IQ	0.09 (0.05-0.12)	<.001
FEP Group	-0.34 (-1.45-0.77)	.547
Time (follow-up)	1.54 (0.22-2.85)	.022
FEP Group x Time	-0.46 (-2.13-1.20)	.582

Abbreviations: FEP, First-episode Psychosis; HC, Healthy Control; VPA, Verbal Paired Associates

Discussion

In this longitudinal study of individuals with FEP disorders, we examined changes in visuospatial and verbal associative memory abilities over a follow-up period of 5 to 11 years. Our findings revealed no difference in either visuospatial or verbal associative memory scores in FEP patients relative to HCs at baseline. However, we identified a deteriorating trajectory in visuospatial associative memory compared with healthy controls subjects. In contrast change in verbal associative memory did not differ from controls, with both groups showing improved ability over time.

While previous studies have typically found some aspects of memory to be impaired at illness onset (Bora & Murray 2013; Aas et al. 2014), the results of the current study, and of other similar studies of associative memory (Bartholomeusz et al., 2011; Brewer et al., 2005; Williams, Avery, Woolard, & Heckers, 2012; Wood et al., 2002, 2007), indicate that both visual and verbal associative memory are preserved in the early stages of psychosis. Chronic schizophrenia patients, on the other hand, have been found to demonstrate impairments in both visual (Armstrong, Williams, & Heckers, 2012; Armstrong, Kose, Williams, Woolard, & Heckers, 2012; Donohoe et al., 2008; Touloupoulou, Rabe-Hesketh, King, Murray, & Morris, 2003; Wood et al., 2002) and verbal associative memory (Elvevag et al. 2000;

Toulopoulou et al. 2003), which suggests that associative memory ability may deteriorate over the course of psychotic illness.

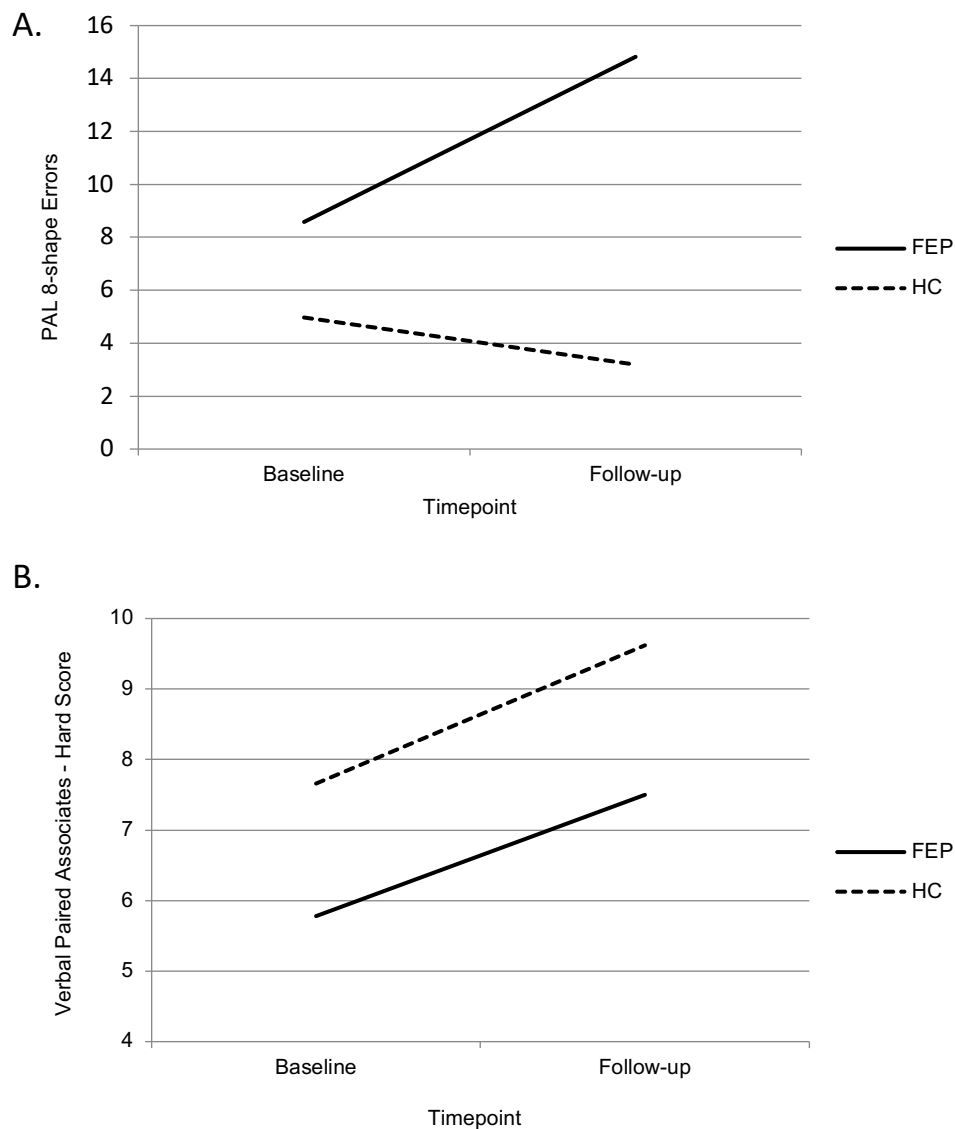


Figure 1. Cognitive performance at baseline and follow-up for (A) PAL 8 shape errors and (B) VPA scores. FEP = first-episode psychosis, HC = healthy control, PAL = Paired Associates Learning, VPA = Verbal Paired Associates.

Consistent with previous cross-sectional findings (Wood et al. 2002; Barnett et al. 2005; Stip et al. 2005; Donohoe et al. 2008), the current study found that visuospatial associative memory ability was preserved at baseline in the FEP cohort. In this first longitudinal study of PAL performance from psychosis onset, visuospatial associative memory ability deteriorated

significantly over a 5-11 year follow-up period in patients having a schizophrenia spectrum disorder at baseline. Deterioration in visuospatial associative memory challenges the ‘dominant’ notion of stable cognitive deficits in schizophrenia (Bora & Murray 2013), and highlights that different areas of cognition may have different trajectories over the course of psychotic illness. That is, while some cognitive domains are impaired at the earliest stages of the illness, other areas of cognition are preserved at illness onset and deteriorate only as the illness progresses (Pantelis, Wannan, Bartholomeusz, Allott, & McGorry, 2015). In order to understand these differing trajectories, it is important to consider individual cognitive tasks within the context of normal development, while also taking into account the brain changes that have been found to occur in the period following illness onset (Pantelis et al., 2005; Pantelis, Yucel, et al., 2009; Pantelis, Wannan, Bartholomeusz, Allott, & McGorry, 2015).

We have previously argued that there is an interaction between the age of illness onset and stage of brain development, which may result in a relatively greater impact on brain structures and functions that are maturing around the time of illness onset (Gogtay, Vyas, Testa, Wood, & Pantelis, 2011; Pantelis et al., 2005; Pantelis, Yucel, et al., 2009; Pantelis et al., 2015). Thus, areas of cognition that are continuing to mature are likely to have their development interrupted by illness onset, whereas areas of cognition that develop early, prior to illness onset, may be preserved. Spatial working memory ability, for example, which typically does not fully mature until the mid-20s (De Luca et al. 2003), and may therefore be interrupted by psychosis onset, has been found to be impaired to a similar extent in FEP patients and chronic schizophrenia patients (Pantelis, Wood, et al., 2009; Wood et al., 2002). Conversely, associative memory ability develops early in life, with performance increasing steeply between ages 8 and 11 and plateauing thereafter (Thaler et al. 2013). It is possible that this ability has finished maturing prior to illness onset, and is therefore unaffected in the early stages of the illness. This was also observed on a task of attentional set-shifting ability (Pantelis, Wood, et al., 2009), which also matures early (De Luca et al. 2003).

Deterioration of visuospatial associative memory following psychosis onset may be related to brain abnormalities observed in individuals with psychosis. The brain network that is implicated in performance on the PAL task is the hippocampal-prefrontal pathway (De Rover

et al. 2011; Barnett et al. 2016) which has been shown to be disrupted in individuals with schizophrenia (Sigurdsson & Duvarci 2015). Activity in this pathway is highly sensitive to stress (Godsil et al. 2013), and it is therefore possible that the acute stress experienced at the onset of psychosis may lead to increasingly aberrant functional coupling between the hippocampus and prefrontal cortex and, consequently, deteriorating visuospatial associative memory ability. Furthermore, longitudinal studies of brain structure in individuals with schizophrenia have identified progressive loss of grey matter in regions relevant to the PAL task, including in the prefrontal cortex and the medial temporal lobe (Bartholomeusz et al., 2016; Radua et al., 2012; Vita, De Peri, Deste, & Sacchetti, 2012). Thus, while visuospatial associative memory ability is preserved at the time of illness onset, progressive deterioration, both structurally and functionally, in brain regions relevant to this area of cognition may impact on functioning as the illness progresses.

Further, we found that visuospatial associative memory performance at baseline and follow-up was associated with functional outcome at follow-up. A previous study of FEP patients by Barnett et al. (2005) found that individuals who failed this same task scored higher on negative symptom and psychopathology measures, had poorer levels of global functioning, and higher disability scores. In chronic patients, visuospatial associative memory performance at baseline predicted improvement in daily living autonomy and social competence following participation in a rehabilitation program (Prouteau et al. 2005). The current study adds to these findings by demonstrating that visuospatial associative memory ability early in a psychotic illness can predict social and occupational functioning over long follow-up periods of 5-11 years. Thus, poor performance on this task at the time of psychosis onset may help identify individuals having poor long-term functional outcome. In contrast, baseline performance on the verbal paired-associates was not associated with later social and occupational functioning, suggesting that its use as a predictive tool is limited in psychosis populations.

The observed deterioration of visuospatial associative memory contrasts with the relatively preserved verbal associative memory performance observed over the same period in the FEP cohort. Thus, the observed improvement in verbal associative memory over time was in

accord with improved ability in controls. While a number of longitudinal studies have observed similar improvement in verbal memory performance following psychosis onset (Rodríguez-Sánchez et al. 2013; Olivier et al. 2015), what differentiates the current findings from those of the majority of previous studies is that, after accounting for general intellectual impairment, the patient group did not demonstrate deficits on the verbal associative memory task at either baseline or follow-up. While this result is surprising, it is in line with an earlier cross-sectional study of verbal memory abilities in FEP patients and individuals with chronic schizophrenia (Wood et al. 2007), which found preserved verbal associative memory ability in both patient cohorts relative to healthy controls. Preservation of verbal associative memory may simply be related to the relative ease of the VPA task compared to the PAL task. That is, this task may not be sensitive enough to psychosis-related brain abnormalities to detect memory impairments above and beyond those that result from generalised intellectual impairment. The ease of the VPA task may, in-part, reflect the fact that the attentional load of this task is likely to be much lower than that of the CANTAB PAL task. As attention has been found to be highly impaired in individuals with schizophrenia (Aas et al. 2014; Braw et al. 2008; Fioravanti et al. 2012), tasks with a high attentional load are more likely to be impaired in these individuals.

The results of the current study should be considered in the context of several limitations. The small number of participants (particularly healthy individuals) completing the PAL task at follow-up may limit the generalisability of the findings. However, due to the long follow-up duration, a high attrition rate is not unexpected. Additionally, follow-up assessment was only conducted at one time-point, and it is therefore impossible to determine the timing and rate of the changes that were observed in cognitive performance at follow-up. Increasing the number of follow-up time-points would help identify when cognitive changes occur following psychosis onset, and the relative speed with which they occur, especially given brain changes in early illness stages are shown to occur in a relatively short timeframe (Bartholomeusz et al., 2016).

In summary, the current study has found that visuospatial associative memory was preserved at baseline in FEP patients, with significant deterioration occurring over the 5- to 11-year

follow-up period relative to healthy individuals. Baseline performance on the PAL task was also found to be a predictor of later social and occupational functioning. Verbal associative memory, on the other hand, was unimpaired at both time-points, and was found to improve over follow-up to a similar degree observed in healthy controls. Baseline verbal associative memory ability was not associated with functioning at follow-up. These findings highlight the importance of taking the normal maturational trajectories of different areas of cognition into account, with evidence suggesting that areas of cognition that reach maturity earlier in life are likely to be preserved at the time of illness onset, but may be impacted by factors relating to the illness or its treatment, leading to deterioration of these abilities over time. These findings may also have implications for the remediation strategies used to treat cognitive impairments in schizophrenia; while these strategies have, to date, largely focused on deficits, it is possible that different approaches are required for areas of cognition with different trajectories (Pantelis et al., 2015). Namely, preventing deterioration in areas of cognition that are relatively unaffected at illness onset, particularly those that are closely related to functional outcome, should be an important treatment goal.

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CHAPTER 4:

Hippocampal subfields and visuospatial associative memory across stages of schizophrenia-spectrum disorder

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Hippocampal subfields and visuospatial associative memory across stages of schizophrenia-spectrum disorder

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Abstract

Background: While previous studies have identified relationships between hippocampal volumes and memory performance in schizophrenia, these relationships are not apparent in healthy individuals. Further, few studies have examined the role of hippocampal subfields in illness-related memory deficits, and no study has examined potential differences across varying illness stages. The current study aimed to investigate whether individuals with early and established psychosis exhibited differential relationships between visuospatial associative memory and hippocampal subfield volumes.

Methods: Measurements of visuospatial associative memory performance and grey matter volume were obtained from 52 individuals with a chronic schizophrenia-spectrum disorder, 28 youth with recent-onset psychosis, 52 older healthy controls, and 28 younger healthy controls.

Results: Both chronic and recent-onset patients had impaired visuospatial associative memory performance, however only chronic patients showed hippocampal subfield volume loss. Both chronic and recent-onset patients demonstrated relationships between visuospatial associative memory performance and hippocampal subfield volumes in the CA4/dentate gyrus and the stratum that were not observed in older healthy controls. There were no group by volume interactions when chronic and recent-onset patients were compared.

Conclusions: The current study extends the findings of previous studies by identifying particular hippocampal subfields, including the hippocampal stratum layers and the dentate gyrus, that appear to be related to visuospatial associative memory ability in individuals with both chronic and first-episode psychosis.

Introduction

Memory impairments are considered to be a core cognitive dysfunction in schizophrenia, with patients exhibiting deficits across a wide range of memory tasks relative to healthy controls. While it has previously been suggested that memory ability is stably impaired in individuals with schizophrenia (Bora & Murray, 2013), recent longitudinal evidence indicates that one particular type of memory, visuospatial associative memory, is preserved in individuals with first-episode psychosis, with deterioration occurring only as the illness progresses (Haring *et al.* 2017; Wannan *et al.* 2017). It is therefore possible that deficits in visuospatial associative memory observed in chronic patients (Wood *et al.* 2002; Stip *et al.* 2005; Donohoe *et al.* 2008) are related to stage-specific brain abnormalities in regions associated with this ability (Bartholomeusz *et al.* 2016). Given that deficits in visuospatial associative memory have previously been associated with both concurrent and prospective functional impairment in individuals with first-episode and established psychotic illness (Barnett *et al.* 2005; Prouteau *et al.* 2005; Wannan *et al.* 2017), identifying the specific brain regions involved in this ability may be an important first step toward identifying potential underlying mechanisms or treatment targets for deficits in episodic memory that lead to impaired functioning in psychosis.

Visuospatial associative memory ability is thought to be heavily reliant on medial temporal lobe structures, particularly the hippocampus (Barnett *et al.* 2016). In healthy individuals and those in the early stages of Alzheimer's disease, visuospatial associative memory performance has been associated with bilateral hippocampal activation, with increased activation occurring alongside increasing memory load in healthy individuals (Gould *et al.* 2005; De Rover *et al.* 2011). Lesion studies also show that neurosurgical patients who have undergone amygdalo-hippocampectomy demonstrate significant impairments on tasks of visuospatial associative memory (Owen *et al.* 1995). Thus, there is evidence for the involvement of the hippocampus in visuospatial associative memory, although it is unclear whether this extends to measures of hippocampal volume as well as activation.

In individuals with schizophrenia, structural brain abnormalities have consistently been observed in brain regions that are associated with visuospatial associative memory. Bilateral hippocampal volume loss is well established in individuals with chronic schizophrenia (Velakoulis *et al.* 1999; Wright *et al.* 2000; Zakzanis *et al.* 2000; Wood *et al.* 2001; Shepherd

et al. 2012; van Erp *et al.* 2016). While these findings are less consistent in recent-onset patients, several studies have shown left (Velakoulis *et al.* 1999), right (Fornito *et al.* 2009), and bilateral (Copolov *et al.* 2000; Steen *et al.* 2006; Vita *et al.* 2006) hippocampal volume loss in early illness. Additionally, the hippocampus consists of several functionally distinct subfields, including the Cornu Ammonis regions (CA1-4), the dentate gyrus, the subiculum, and the stratum layers, (Duvernoy 1998). High-resolution magnetic resonance imaging (MRI) has revealed a pattern of progressive involvement of hippocampal subfields with increasing illness chronicity in schizophrenia (Mathew *et al.* 2014; Haukvik *et al.* 2015; Ho *et al.* 2016; Baglivo *et al.* 2018). Namely, in first-episode patients volume loss appears to be restricted to hippocampal subfields in the left hemisphere (Baglivo *et al.* 2018), whereas in chronic patients volume loss occurs bilaterally, across most or all investigated hippocampal subfields (Mathew *et al.* 2014; Haukvik *et al.* 2015; Ho *et al.* 2016).

Given that abnormalities of the hippocampus are considered to be among the most robust findings in schizophrenia, it is unsurprising that a number of studies have attempted to elucidate potential relationships between hippocampal volume and memory ability in this population. In individuals with first-episode psychosis (Hasan *et al.* 2011; Lappin *et al.* 2013) and chronic schizophrenia (Gur *et al.* 2000; Nestor *et al.* 2007), larger hippocampal volumes have been associated with superior memory performance. In healthy individuals however, relationships between hippocampal volumes and memory performance appear to be absent or attenuated (Van Petten 2004; Den Heijer *et al.* 2012; Lappin *et al.* 2013), suggesting that these relationships may be moderated by hippocampal pathology unique to patient groups. Of the two known studies correlating hippocampal subfield volumes with memory in schizophrenia, one found that smaller subiculum volumes were associated with poorer verbal memory performance (Haukvik *et al.* 2015), and the other found that left CA1, CA2/CA3, subiculum, and CA4/dentate gyrus volumes were positively correlated with list-learning (Mathew *et al.* 2014). However, while these findings provide initial evidence for the involvement of particular hippocampal subfields for memory performance in schizophrenia, it remains unclear whether these relationships are present at earlier illness stages, and whether similar results may be seen with measures of visuospatial associative rather than verbal memory.

The current study aimed to investigate relationships between visuospatial associative memory and hippocampal subfield volumes in early and established psychosis. The specific aims of

the study were to (i) evaluate whether chronic schizophrenia patients and youth with recent-onset psychosis differed in visuospatial associative memory performance, and hippocampal subfield volumes, in comparison to healthy controls and each other, and (ii) to determine whether these patient groups exhibited differential relationships between hippocampal subfield volumes and visuospatial associative memory, compared to healthy controls and to each other. We predicted that chronic patients would exhibit severe impairments in visuospatial associative memory relative to both recent-onset patients and older healthy controls, whereas recent-onset patients would perform at a similar level to younger healthy controls. We also expected to find widespread hippocampal subfield volume loss in chronic patients, relative to both recent-onset patients and healthy controls. Finally, we expected to find stronger relationships between visuospatial associative memory and hippocampal subfield volumes in patient groups relative to healthy controls, and stronger relationships in chronic patients relative to recent-onset patients.

Method

Participants

Fifty-two individuals with a chronic schizophrenia-spectrum disorder (illness duration > 5 years) and 28 youth with recent-onset psychosis (< 2.5 years since first presentation to a mental health service for treatment of psychosis, number of psychotic episodes $\geq$ 1) were recruited as part of two separate studies. Recent-onset patients were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne, Australia. EPPIC is a specialised public mental health service for people aged 15–25 years living in the north-western suburbs of metropolitan Melbourne who have experienced a first episode of psychosis. EPPIC intake criteria include: first presentation of suspected psychotic illness, or less than six-months previous antipsychotic treatment for a first psychotic episode. Chronic patients were recruited from inpatient (20%) and outpatient (80%) clinics in Melbourne, Australia. Study measures were identical across both studies, except for diagnostic and symptom measures. All patients were diagnosed with a schizophrenia-spectrum disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 1994). Diagnoses were confirmed using either The Mini International Neuropsychiatric Interview (MINI; Sheehan *et al.*, 1998) or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First *et al.* 2002).

Two groups of age-matched healthy control participants with similar socioeconomic and educational backgrounds were recruited from the general community using online advertising: young controls ($n = 28$; mean age of 21.96), and older controls ($n = 52$; mean age of 38.62). The MINI or the SCID were used to rule out current or past history of psychopathology in healthy controls.

Exclusion criteria for all participants were (1) a history of head injury or seizures, (2) diagnosis of a neurological disorder, (3) pregnancy, and (4) contraindication to MRI scanning. Additional exclusion criteria specific to healthy controls included personal and first-degree relatives with a history of psychotic illness. All participants were either native English speakers or were fluent in English as determined by their self-report of numbers of years learnt English or schooled in English. Five older healthy controls, 4 younger healthy controls, and 3 recent-onset patients came from non-English speaking backgrounds. When analyses were re-run following removal of four older healthy controls who did not receive any formal education in English results remained unchanged.

The studies were approved by the Melbourne Health (2012.066, 2012.069) and Austin Health (H2012/04525) Human Research Ethics Committees and all participants provided written informed consent prior to participation.

Clinical measures

Negative symptoms in both patient cohorts were measured using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Positive symptoms were measured using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) or the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). PANSS scores were converted to BPRS scores (Leucht *et al.* 2013), in order to provide a measure of general psychopathology and positive symptoms. Each participants' functioning was evaluated using the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman, Skodol, & Lave, 1992). Current IQ was measured using the 2-subtest short form (Vocabulary and Matrix Reasoning) of the WAIS-III (Wechsler 1997). The Wechsler Test of Adult Reading (Wechsler 2001) was used to estimate premorbid IQ.

Neuropsychological assessment

Visuospatial associative memory was measured using the Visuospatial Paired-Associate Learning (PAL) Task from the CANTAB (Cambridge Cognition 2016). Details of this task have been described previously (Wannan *et al.* 2017). The total number of trials required to locate all of the patterns correctly in all stages of the task was the variable of interest, and therefore lower scores are better. For participants who did not complete all stages (due to failing at an earlier stage), the maximum score of 10 trials was added to their score for each stage that was not completed (Cambridge Cognition 2012).

Imaging data acquisition

Magnetic resonance images were acquired on a Siemens Avanto 3T Magnetom TIM Trio scanner. T1-weighted images were acquired using an optimized Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence. The sequence parameters were: 176 sagittal slices of 1 mm thickness without gap, field of view (FOV) = $250 \times 250 \text{ mm}^2$, repetition time (TR)=1980 ms, echo time (TE) = 4.3 ms, flip angle = 15° , using an acquisition matrix of 256×256 resulting in a final reconstructed voxel resolution of $0.98 \times 0.98 \times 1.0 \text{ mm}^3$.

Image processing

Intracranial volume (ICV) was estimated using FreeSurfer version 5.3 (<http://surfer.nmr.mgh.harvard.edu>)(Fischl *et al.* 2004). FreeSurfer determines estimated ICV using an atlas scaling factor (i.e. the determinant of an affine transformation matrix) derived from registering images to an average template using a full (12-parameter) affine transformation (Malone *et al.* 2015). For detailed information, see Buckner *et al.*, 2004. Fully-automated segmentation of the hippocampus was carried out using the MAGeT Brain algorithm (Chakravarty *et al.*, 2013: [//github.com/CobraLab/MAGeTbrain](https://github.com/CobraLab/MAGeTbrain)). This modified multi-atlas segmentation technique is designed to use a limited number of high-quality manually segmented atlases of the hippocampal subfields as input (Pipitone *et al.* 2014). These atlases include definitions for the right and left CA1, CA2CA3, CA4/dentate gyrus (CA4DG), strata radiatum/lacunosum/moleculare (stratum), and subiculum (see Figure 1). Atlas segmentations are propagated to a template library and then to subjects using nonlinear registration (Avants *et al.* 2008), and a subset of the population under study is used as the template library through which the final segmentation is bootstrapped. Each subject in the template library is segmented through nonlinear atlas-to-template registration followed by label propagation, yielding 5 unique definitions of the hippocampus for each of the templates.

In the current study, 21 templates, consisting of ten controls and eleven patients, were selected based on age and gender to ensure a representative template set. This resulted in 105 candidate labels for each subject, and labels were then fused using a majority vote to complete the segmentation process. As the dentate gyrus and subiculum are included within the MAGEt Brain algorithm, the term “hippocampus” used throughout this manuscript encompasses the hippocampal formation. Quality assurance for each scan was carried out at three time points. First, unprocessed minc files were visually inspected for abnormalities and to ensure image quality and orientation. Second, following data pre-processing, scans were inspected to ensure successful registration to MNI space and inhomogeneity correction. Finally, following processing with MAGEt Brain, each participant’s hippocampal subfield segmentation was visually inspected to ensure segmentation quality using a three point system: 0 = fail; 0.5 = good pass; 1 = excellent pass (for more information on our detailed quality control procedure see Amaral *et al.*, 2018).

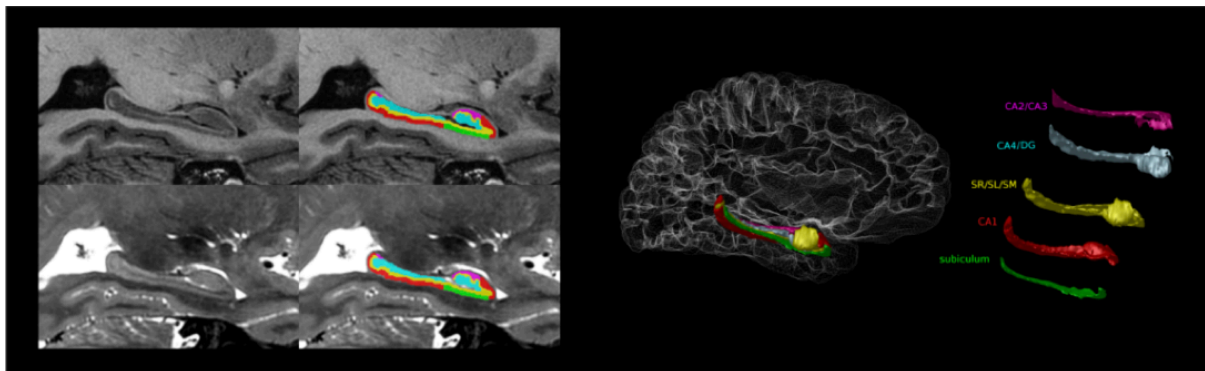


Figure 1. Visualisation of hippocampal subfield segmentation in a single subject, with each subfield represented by a different colour. Reprinted with permission from Winterburn *et al.*, 2013.

Data Analysis

Data were analysed using SPSS version 24.

Analysis of demographic data

Group differences on demographic measures were examined using chi-square tests for categorical data, and t-tests for continuous variables.

Analysis of PAL data

The number of trials required to complete the PAL task was compared between groups using robust generalized linear models, with age and IQ included as covariates. Three separate

analyses were conducted: recent-onset vs younger controls, chronic vs older controls, recent-onset vs chronic. Chi square tests were also used to compare the number of individuals who passed or failed the PAL task in each group.

Between-group differences in hippocampal volumes

ANCOVAs were used to compare total hippocampal and hippocampal subfield volumes between groups, with age, sex and ICV included as covariates. Three separate analyses were conducted: recent-onset vs younger controls, chronic vs older controls, recent-onset vs chronic. Results were corrected for multiple comparisons across each hemisphere using a False Discovery Rate (FDR) of $p < .05$ (Benjamini & Hochberg 1995).

Interactions between hippocampal subfield volumes and group

In order to determine whether differential relationships existed between visuospatial memory ability and hippocampal subfield volumes between groups, a series of robust generalized linear models were conducted. Each model included main effects of group and volume and any group $\times$ volume interactions, with age and ICV included as covariates. Main effects of volume and group $\times$ volume interactions were the outcomes of interest. Results were corrected for multiple comparisons across each hemisphere using a False Discovery Rate (FDR) of $p < .05$ (Benjamini & Hochberg 1995). For regions where there was a significant group $\times$ volume interaction, post-hoc linear models were conducted separately for each group.

Sex was not included as a covariate in the analysis of PAL data as there were no between-group differences in PAL performance for males and females, and all groups were well matched for sex. Medication and illness duration were also considered as covariates when comparing the two patient groups. However as neither current antipsychotic dosage nor illness duration was correlated with either hippocampal subfield volumes or performance on the PAL task in either recent-onset or chronic patients, these were not included in further analyses.

Results

Demographic results

Demographic data are displayed in Table 1. There were no group differences for age or sex between the two patient groups and their respective healthy control groups. Chronic patients

Table 1. Demographics

	Group				t-statistic/ χ^2		
	FEP	Younger HC	Chronic	Older HC	FEP vs. Younger HC	Chronic vs. Older HC	FEP vs. Chronic
Age	21.37 (2.00)	21.96 (1.96)	38.55 (9.21)	39.15 (10.43)	t = 1.19	t = -0.32	t = 12.92**
Gender (M/F)	21/7	18/10	38/14	33/18	$\chi^2 = 0.76$	$\chi^2 = 0.84$	$\chi^2 = 0.04$
Current IQ	95.50 (17.29)	118.89 (9.56)	86.20 (19.52)	115.32 (11.13)	t = 6.27**	t = 8.95**	t = 2.10*
Premorbid IQ	99.25 (15.41)	112.36 (11.87)	93.72 (14.41)	107.89 (8.82)	t = 3.57**	t = 5.74**	t = 1.56
Years of education	12.59 (2.45)	15.11 (1.92)	12.14 (3.05)	16.29 (2.79)	t = 4.25**	t = 6.82**	t = 0.66
SOFAS	56.14 (10.04)	85.79 (7.03)	46.69 (14.00)	79.29 (10.98)	t = 12.80**	t = 11.17**	t = 3.13**
Illness duration (years)	1.78 (0.84) [#]	-	16.69 (7.88)	-	-	-	-
Illness duration quartiles (25/75%)	1.10/2.33 [#]	-	10.50/21.50	-	-	-	-
CPZ equivalent	415.16 (444.61)	-	1045.76 (656.83)	-	-	-	t = 4.40**
Positive symptoms	12.93 (4.85)	-	16.96 (5.96)	-	-	-	t = 3.06**
Negative symptoms	23.42 (13.03)	-	40.04 (17.77)	-	-	-	t = 4.30**

* $p < .05$ ** $p < .01$ [#] For FEP patients, illness duration includes both duration of full-threshold and prodromal symptoms

Abbreviations: FEP, first-episode psychosis; HC, healthy control; SOFAS, Social and Occupational Functioning Assessment Scale; CPZ, chlorpromazine

Table 2. Between-group comparisons of hippocampal subfield volumes

Hemisphere	Subfield	FEP		Younger HC		Chronic		Older HC		F statistic			Partial Eta Squared (90% CI)		
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	FEP vs. Younger HC	Chronic vs. Older HC	FEP vs. Chronic	FEP vs. Younger HC	Chronic vs. Older HC	FEP vs. Chronic
Left	CA1	730.89	65.80	740.14	78.91	754.41	93.37	767.31	103.91	0.03	2.76	0.988	0.001 (0-0.04)	0.03 (0-0.10)	0.01 (0-0.08)
	Subiculum	332.13	30.32	348.21	47.82	342.42	41.05	344.56	38.48	0.58	1.19	0.004	0.01 (0-0.10)	0.01 (0-0.07)	0.00 (0-0.00)
	CA4/DG	647.16	72.43	695.19	75.39	618.00	73.63	684.07	92.48	3.77	36.65*	1.124	0.07 (0-0.20)	0.27 (0.15-0.38)	0.02 (0-0.09)
	CA2/CA3	147.20	25.10	151.59	25.82	138.44	27.07	150.92	27.66	0.06	8.77*	2.797	0.001 (0-0.05)	0.08 (0.02-0.18)	0.04 (0-0.13)
	Stratum	603.42	63.19	618.64	68.16	569.70	70.77	608.68	89.79	0.16	11.80*	2.114	0.003 (0-0.07)	0.11 (0.03-0.21)	0.03 (0-0.12)
Right	CA1	740.93	66.89	772.71	95.04	832.87	101.07	842.47	111.04	1.10	2.64	9.29*	0.02 (0-0.12)	0.03 (0-0.10)	0.11 (0.02-0.23)
	Subiculum	322.27	39.50	329.31	45.55	322.55	50.29	330.78	41.45	0.04	3.04	1.536	0.001 (0-0.043)	0.03 (0-0.10)	0.02 (0-0.10)
	CA4/DG	646.31	77.36	695.96	83.84	639.55	72.91	689.19	84.30	2.68	28.47*	0.008	0.05 (0-0.17)	0.22 (0.11-0.33)	0.00 (0-0.01)
	CA2/CA3	161.82	29.33	168.51	22.16	173.49	30.40	186.51	25.80	0.14	12.2*	2.373	0.003 (0-0.07)	0.11 (0.03-0.21)	0.03 (0-0.12)
	Stratum	574.00	63.61	613.29	81.91	548.86	77.51	582.35	84.35	2.25	10.84*	2.103	0.04 (0-0.16)	0.10 (0.02-0.20)	0.03 (0-0.11)

* $p < .05$, FDR corrected

Abbreviations: FEP, first-episode psychosis; HC, healthy control

were significantly older than recent-onset patients. Both patient groups had significantly lower current IQ, premorbid IQ, years of education, and SOFAS scores compared to their respective healthy control groups. Chronic patients also had significantly lower current IQ and SOFAS scores than recent-onset patients, however there were no differences in premorbid IQ or years of education between patient groups. Chronic patients also had higher positive and negative symptom scores and antipsychotic doses than recent-onset patients. Although there were group differences in IQ, it is difficult to disentangle these effects from the disorder itself due to the intrinsic nature of IQ deficits to schizophrenia-spectrum illnesses (Kahn & Keefe 2013). When a particular variable is an attribute of a disorder, or intrinsic to the condition, it is suggested to be meaningless to include this variable as a covariate (Tupper & Rosenblood 1984; Miller & Chapman J 2001; Dennis *et al.* 2009). Therefore, IQ was not included as a covariate in any of the regression models.

Neuropsychological results

As seen in Figure 2, Chronic patients required significantly more trials than older healthy controls on the PAL task, Wald $\chi^2 = 30.83$, $p < .0001$, ($\exp(\beta) = 730.25$ (95% CI: 71.22-7487.35)). Chronic patients were also significantly more likely to fail the PAL task compared to older controls, $\chi^2 = 30.31$, $p < .0001$. recent-onset patients required significantly more trials than younger healthy controls on the PAL task, Wald $\chi^2 = 4.59$, $p = .032$, ($\exp(\beta) = 13.21$ (95% CI: 1.25-140.02)), however, they were no more likely than healthy controls to fail the PAL task $\chi^2 = 1.98$, $p = .16$. There was no difference between chronic and recent-onset patients for number of trials required on the PAL task, Wald $\chi^2 = 1.73$, $p = .188$, ($\exp(B) = 13.56$ (95% CI: 0.28-657.85)), however chronic patients were significantly more likely to fail to complete the PAL task than were recent-onset patients, $\chi^2 = 11.20$, $p = <.001$. Number of trials required to complete the PAL task for each group are displayed in Figure 2.

Between-group differences in hippocampal volumes

Chronic patients had reduced volumes in the CA4DG, CA2CA3, and stratum bilaterally, and in the right subiculum relative to older healthy controls (see Table 2). There were no differences between recent-onset patients and younger healthy controls for any subfield volume in either hemisphere. There were also no differences between recent-onset and chronic patients for any subfield volumes except for the right CA1, where recent-onset patients had volume reductions compared to chronic patients.

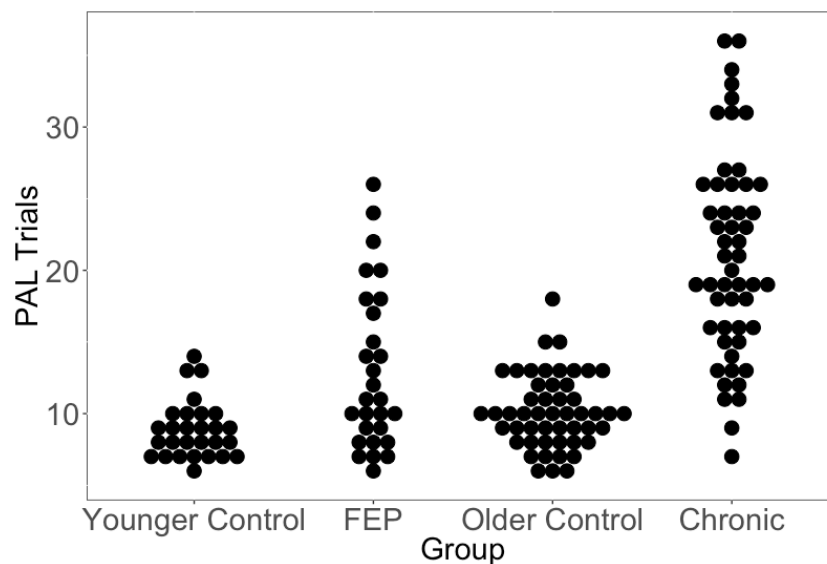


Figure 2. Number of trials required to complete the Paired Associates Learning task for younger healthy controls, first-episode psychosis patients, older healthy controls, and chronic schizophrenia-spectrum patients

Interactions between hippocampal subfield volumes and group

Recent-onset vs. younger controls

As seen in Figure 3A, significant group $\times$ volume interactions were observed in the left hemisphere for stratum, CA4DG, and CA2CA3 volume. Significant group $\times$ volume interactions were also found in the right hemisphere for CA4DG and stratum volumes. Post-hoc analyses revealed that recent-onset patients had significant negative correlations between hippocampal subfield volumes and number of trials required to complete the PAL task in the left CA4DG and stratum, that were not observed in healthy control subjects. For the left CA2CA3 and the right CA4DG and stratum, recent-onset patients also demonstrated negative correlations with PAL trials that were not observed in healthy individuals, although these did not reach significance. Detailed results are provided in supplementary materials (Table S1).

Chronic vs. older controls

As seen in Figure 3B, significant group $\times$ volume interactions were observed in the right hemisphere for CA1, CA4DG, CA2CA3, and stratum volumes. There was also a significant group $\times$ volume interaction for the left stratum. Post-hoc analyses revealed that chronic patients had significant negative correlations between hippocampal subfield volumes and number of trials required to complete the PAL task in the right CA4DG, and in the stratum bilaterally, that were not observed in healthy control subjects. For the right CA1, chronic

patients also demonstrated a negative correlation with PAL trials that were not observed in healthy individuals, although this did not reach significance. Older healthy controls also demonstrated a significant positive relationship between right CA2CA3 volume and PAL trials that was not observed in chronic patients. Detailed results are provided in supplementary materials (Table S2).

Chronic vs. recent-onset

There were no significant group $\times$ volume interactions for chronic and recent-onset patients in any subfield region. However, there were significant main effects of volume for the left CA4DG and stratum, with larger subfield volumes associated with better performance on the PAL task. Detailed results are provided in supplementary materials (Table S3).

Discussion

In this study, we examined visuospatial associative memory ability and hippocampal subfield volumes in individuals with recent-onset and chronic schizophrenia as well as their relationships. Both chronic patients and youth with recent-onset psychosis had impaired visuospatial associative memory performance, however, only chronic patients showed hippocampal subfield volume loss relative to healthy controls. recent-onset and chronic patients also demonstrated negative relationships between the number of trials required to complete the PAL task and hippocampal subfield volumes that were not observed in their respective healthy control groups, suggesting that smaller hippocampal subfields were associated with poorer visuospatial associative memory in both early and late illness stages. There were no group $\times$ volume interactions for any hippocampal subfield when recent-onset and chronic patients were compared with each other.

Visuospatial associative memory performance

Contrary to our hypothesis, both chronic and recent-onset patients required significantly more trials than their respective healthy control groups to complete the PAL task. There was also no group difference in performance between chronic and recent-onset patients once age was taken into account. However, chronic patients were significantly more likely to fail to complete the PAL task than recent-onset patients, and there were no differences in pass rates between recent-onset patients and younger controls. Thus, although the recent-onset patients demonstrate visuospatial associative memory impairments, these appear to be milder than

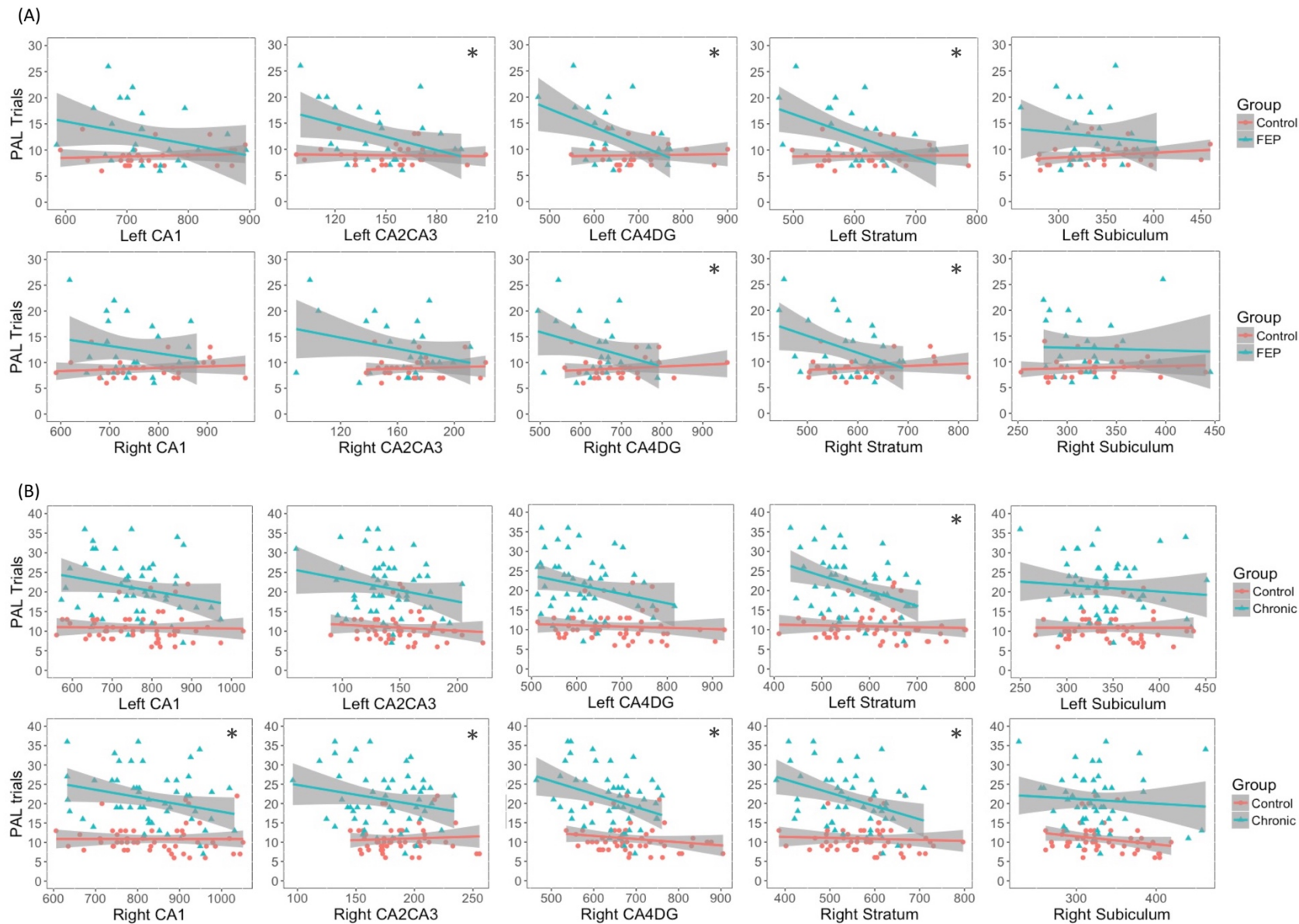


Figure 3. Relationships between hippocampal subfield volumes and group for number of trials required to complete the Paired Associated Learning task, in (A) first-episode psychosis patients and younger healthy controls, and (B) chronic schizophrenia-spectrum patients and older healthy controls. Subfields in which there were significant group $\times$ volume interactions are marked with an asterisk.

those observed in chronic patients. Although previous studies have also identified visuospatial associative memory deficits in individuals with chronic schizophrenia (Wood *et al.* 2002; Stip *et al.* 2005; Donohoe *et al.* 2008), prior studies of recent-onset patients found preserved functioning in this domain (Wood *et al.* 2002; Barnett *et al.* 2005; Wannan *et al.* 2017), with deterioration occurring only after illness onset (Haring *et al.* 2017; Wannan *et al.* 2017). One potential explanation for the visuospatial associative memory deficit in our recent-onset group is their longer duration of illness compared to previous studies (Wood *et al.* 2002; Wannan *et al.* 2017). Given that the most pronounced brain changes in schizophrenia-spectrum illness have been shown to occur in the first 6-12 months following illness onset (Bartholomeusz *et al.* 2016), we might expect that cognitive decline would occur in a similarly short period. With an average illness duration of over 1.5 years (including prodromal illness), it is possible that some deterioration of visuospatial associative memory had already occurred in this patient group, resulting in the observed deficits.

Hippocampal subfield volumes in recent-onset and chronic schizophrenia

Chronic patients had significant volume reductions in several hippocampal subfields, including the bilateral CA4DG, CA2CA3, and stratum, and the right subiculum, relative to older healthy controls. This is consistent with previous studies that identified volume reductions across most hippocampal subfields in chronic schizophrenia (Mathew *et al.* 2014; Haukvik *et al.* 2015; Ho *et al.* 2016). Recent-onset patients on the other hand, did not differ from younger controls in any hippocampal subfield volume. This is contrary to recent findings in which recent-onset patients were shown to have volume reductions across several hippocampal subfields, including the bilateral CA1 and CA4, and the left CA3 (Baglivo *et al.* 2018). Volumes of our recent-onset patients also largely did not differ from chronic patients: the right CA1 was the only subfield in which patient groups differed significantly, with the recent-onset patients demonstrating smaller volumes in this region. The smaller CA1 volume observed in recent-onset patients in the current sample may reflect continuing maturation of this region in the younger patient group: examination of the relationship between age and CA1 subfield volumes in recent-onset and chronic patients revealed that age was positively correlated with CA1 volumes in recent-onset patients, whereas chronic patients exhibited a negative relationship between age and CA1 volumes.

Differential relationships between hippocampal subfield volumes and visuospatial associative memory

Significant group $\times$ volume interactions were observed in virtually identical subfields in the recent-onset and chronic groups relative to controls. Namely, the stratum layers and CA4DG were primarily affected in both groups, implicating these particular subfields as important for visuospatial associative memory performance across illness stages. However the two groups displayed noticeable differences in the laterality of their relationships, with post hoc relationships largely in the left hemisphere in recent-onset patients, and in the right hemisphere for chronic patients. These findings are of particular note given hippocampal volume loss, including in a recent study of hippocampal subfield volumes, has been restricted to the left hemisphere in recent-onset patients (Velakoulis *et al.* 1999, 2006; Baglivo *et al.* 2018) with bilateral volume loss observed only in chronic schizophrenia patients (Velakoulis *et al.* 1999, 2006). These findings suggest that initial deterioration in visuospatial associative memory ability may be related to left hippocampus atrophy in early psychosis, resulting in compensatory use of the right rather than bilateral hippocampus for performance on memory tasks in early illness stages. Ongoing memory deterioration in chronic patients may therefore be related to the spread of pathology to the previously unaffected right hippocampus. It should be noted that despite differences in laterality when compared to their respective healthy control groups, there were no group $\times$ volume interactions in either hemisphere when the two patient groups were analysed together. Thus, recent-onset patients appear to have similar relationships between visuospatial associative memory performance and hippocampal subfield volumes in the right hemisphere to chronic patients, though they may not be quite as strong.

The current study provides evidence for the critical role of the hippocampal stratum layers for visuospatial associative memory in schizophrenia. Differential relationships between stratum volumes and the number of trials required to complete the PAL task were observed in both chronic and recent-onset patients relative to their respective healthy control groups; poorer performance on the PAL task was associated with decreased stratum volumes bilaterally, in both patient groups. However, these relationships were not observed in either healthy control group. The stratum radiatum and stratum lacunar-moleculare layers of the hippocampus contain the apical and terminal dendrites of the CA pyramidal cells respectively, as well as some of the axons of the perforant pathway, which connects the entorhinal cortex to the hippocampus (Witter 2007). Chronic exposure to stress hormones has been shown to cause apical dendritic retraction in the hippocampus (Woolley *et al.* 1990; McEwen 2000), including the stratum radiatum (Chen *et al.* 2010), which in turn leads to impaired spatial

memory ability (Conrad 2006). Indeed, a number of studies have identified relationships between impaired cognitive functioning and abnormalities in the Hypothalamic-Pituitary-Adrenal (HPA) axis, including increased cortisol levels, in individuals with schizophrenia (Lupien 2000; Walder *et al.* 2000; Aas *et al.* 2011). In this context, it is possible that our results support ongoing illness-related stress as having a potential role in both hippocampal and visuospatial associative memory abnormalities in schizophrenia, although further longitudinal studies are needed to fully explore these complex relationships over time.

An additional hippocampal subfield that showed differential relationships with visuospatial associative memory between patient groups and healthy controls was the CA4DG. The dentate gyrus forms part of the perforant pathway that receives inputs from the entorhinal cortex and projects via mossy fibres into CA3 (Amaral *et al.* 2007). This pathway is critical for associative memory formation (Carr *et al.* 2017), and is dependent on glutamate-mediated signalling via N-methyl-D-aspartate (NMDA) receptors (Zola-Morgan & Squire 1993; Lavenex & Amaral 2000) which comprise different subunits, including GluN1 and GluN2s. Post-mortem studies of schizophrenia patients have revealed decreased GluN1 messenger RNA and protein in the dentate gyrus (Gao *et al.* 2000; Law & Deakin 2001; Stan *et al.* 2015) but not in other hippocampal subfields (Stan *et al.*, 2015), which may suggest a unique pathology of dentate gyrus glutamate function in schizophrenia. This specific dentate gyrus pathology may exert downstream effects on the CA3 (Tamminga *et al.* 2012), which is itself an important region for the encoding of spatial information and the acquisition of relational associations (Kesner 2007), which are both key aspects of visuospatial associative memory. Additionally, the granule cell layer of the dentate gyrus is a site of adult neurogenesis in humans; these adult-born neurons are thought to play a crucial role in episodic memory formation (Benarroch 2013; Drew *et al.* 2013; Gonçalves *et al.* 2016), particularly for spatial memories (Snyder *et al.* 2005). In individuals with schizophrenia however, there is evidence for reduced proliferation of adult-born dentate gyrus granule cells (Allen, Fung, & Weickert, 2016; Reif *et al.*, 2006), which may contribute to both hippocampal volume reductions and memory impairments in this population.

Our findings should be considered in the context of several limitations. Cumulative exposure to antipsychotic medication was not measured in the current study, and therefore it was not possible to control for the effects of ongoing exposure to medication in our analyses. Additionally, for recent-onset patients, duration of illness included both duration of

prodromal and full-threshold symptoms. Furthermore, the lack of association between hippocampal measures and PAL performance in healthy control subjects may be due, in part, to ceiling effects rather than a lack of involvement of these regions for visuospatial associative memory performance in healthy people; Almost all of the healthy controls successfully completed the PAL task. The use of volumetric data in the current study also means that it is not possible to disentangle the potentially unique effects of factors such as hippocampal shape and grey matter surface area and thickness on PAL performance. Previous studies also suggest that the reliability and validity of hippocampal volume estimates may be influenced by the size of each individuals' hippocampi, resulting in over- or under-estimation of volumes for those with larger or smaller hippocampi (Sánchez-Benavides *et al.* 2010; Wenger *et al.* 2014; Schmidt *et al.* 2018). However, this issue was tested in a previous validation of the MAgE Brain segmentation technique, and was not found to be true, with good estimation observed in individuals with small hippocampi (Pipitone *et al.* 2014). Finally, the current study was cross-sectional in nature and therefore unable to identify longitudinal relationships between PAL performance and hippocampal volume changes. Future studies that track changes in visuospatial associative memory ability and brain structure over time would therefore be beneficial.

In conclusion, the current study found that both chronic schizophrenia-spectrum patients and youth with recent-onset psychosis had impaired visuospatial associative memory performance, however only chronic patients showed hippocampal subfield volume loss relative to controls. Further, we identified relationships between visuospatial associative memory performance and hippocampal subfield volumes in recent-onset and chronic schizophrenia patients that were not present in healthy controls. In patients, poorer performance on the PAL task was associated with reductions in hippocampal subfield volumes, primarily in the stratum layers and the CA4DG. In recent-onset patients, these relationships were observed in the left hemisphere, whereas in chronic patients findings were bilateral. Furthermore, when patient groups were compared, differential relationships between hippocampal subfield volumes and PAL performance were not observed, suggesting that similar hippocampal-memory relationships are present in both early and established illness. The current study extends the findings of previous studies that have examined relationships between hippocampal volume reductions and memory impairment in schizophrenia (Sanfilipo *et al.* 2002; Touloupoulou *et al.* 2004; Exner *et al.* 2008; Thoma *et al.* 2009) by identifying particular hippocampal subfields that appear to be related to visuospatial

associative memory ability in individuals at early and late stages of a schizophrenia-spectrum illness. Further longitudinal studies that map progression of visuospatial associative memory ability and hippocampal subfield volumes from the prodromal illness stage would help to tease out how these two variables interact over time.

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Hippocampal subfields and visuospatial associative memory across stages of schizophrenia-spectrum disorder

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Supplementary Material

Supplementary Table 1. Robust General linear model examining the effects of volume and group x volume interactions on visuospatial associative memory in first-episode patients and younger healthy controls

	Volume		Group X Volume		Post hoc tests			
					First-episode psychosis		Younger controls	
	Wald χ^2	Exp. B (95% CI)	Wald χ^2	Exp. B (95% CI)	Wald χ^2	Exp. B (95% CI)	Wald χ^2	Exp. B (95% CI)
Left CA1	0.84	1.01 (0.99-1.02)	3.86	0.98 (0.95-1.00)				
Left subiculum	2.27	1.02 (0.99-1.04)	0.41	0.98 (0.93-1.04)				
Left CA4DG	0.32	1.00 (0.99-1.02)	12.80*	0.96 (0.94-0.98)	6.13*	0.97 (0.94-0.99)	0.02	1.00 (0.99-1.01)
Left CA2CA3	0.16	1.01 (0.98-1.03)	5.10*	0.91 (0.84-0.99)	3.57	0.92 (0.84-1.00)	0.13	0.99 (0.97-1.02)
Left stratum	0.12	1.00 (0.99-1.02)	8.81*	0.96 (0.93-0.99)	5.43*	0.96 (0.93-0.99)	0.06	1.00 (0.99-1.01)
Right CA1	1.54	1.01 (0.99-1.02)	1.49	0.98 (0.95-1.01)				
Right subiculum	2.17	1.02 (0.99-1.05)	0.17	0.99 (0.93-1.05)				
Right CA4DG	0.62	1.01 (0.99-1.02)	5.64*	0.97 (0.95-1.00)	2.83	0.97 (0.95-1.00)	0.38	1.00 (0.99-1.01)
Right CA2CA3	0.48	1.01 (0.98-1.05)	2.65	0.93 (0.85-1.02)				
Right stratum	0.81	1.01 (0.99-1.02)	6.22*	0.96 (0.93-0.99)	3.11	0.97 (0.93-1.00)	0.36	1.00 (0.99-1.02)

* $p < .05$

Supplementary Table 2. Robust General linear model examining the effects of group, volume, and group x volume interactions on visuospatial associative memory in chronic patients and older healthy controls

					Post hoc tests			
	Volume		Group X Volume		Chronic		Older controls	
	Wald χ^2	Exp. B (95% CI)	Wald χ^2	Exp. B (95% CI)	Wald χ^2	Exp. B (95% CI)	Wald χ^2	Exp. B (95% CI)
Left CA1	0.63	1.00 (0.99-1.01)	2.91	0.98 (0.96-1.00)				
Left subiculum	0.31	1.01 (0.98-1.03)	0.52	0.98 (0.93-1.04)				
Left CA4DG	0.35	1.00 (0.99-1.01)	3.36	0.98 (0.96-1.00)				
Left CA2CA3	0.05	1.00 (0.98-1.03)	3.23	0.94 (0.88-1.01)				
Left stratum	0.07	1.00 (0.99-1.01)	8.07*	0.96 (0.94-0.99)	6.35*	0.96 (0.94-0.99)	0.13	1.00 (0.99-1.01)
Right CA1	0.73	1.01 (0.99-1.02)	4.64*	0.98 (0.96-0.99)	2.69	0.98 (0.96-1.00)	1.04	1.01 (0.99-1.02)
Right subiculum	0.53	0.99 (0.97-1.01)	0.62	0.98 (0.94-1.023)				
Right CA4DG	0.26	1.00 (0.99-1.01)	5.58*	0.97 (0.95-0.99)	5.12*	0.97 (0.94-0.97)	0.24	1.00 (0.99-1.01)
Right CA2CA3	3.35	1.04 (1.00-1.09)	4.48*	0.93 (0.87-0.99)	0.71	0.97 (0.91-1.04)	4.15*	1.04 (1.00-1.07)
Right stratum	0.02	1.00 (0.99-1.01)	8.22*	0.97 (0.94-0.99)	6.84*	0.96 (0.94-0.99)	0.15	1.00 (0.99-1.01)
* $p < .05$								

Supplementary Table 3. Robust general linear model examining the effects of volume and group x volume interactions on visuospatial associative memory in first-episode and chronic patients

	Volume		Group X Volume	
	Wald χ^2	Exp. B (95% CI)	Wald χ^2	Exp. B (95% CI)
Left CA1	1.80	0.98 (0.96-1.01)	0.61	1.01 (0.98-1.04)
Left subiculum	0.00	1.00 (0.94-1.07)	0.89	1.00 (0.92-1.07)
Left CA4DG	7.85*	0.97 (0.95-0.99)	0.19	1.02 (0.99-1.05)
Left CA2CA3	3.83	0.92 (0.85-1.00)	0.57	1.03 (0.93-1.14)
Left stratum	7.51*	0.96 (0.93-0.99)	0.64	1.01 (0.97-1.05)
Right CA1	0.56	0.99 (0.95-1.02)	0.98	1.00 (0.96-1.04)
Right subiculum	0.02	1.01 (0.94-1.07)	0.53	0.98 (0.91-1.05)
Right CA4DG	2.90	0.98 (0.95-1.00)	1.00	1.00 (0.97-1.03)
Right CA2CA3	1.25	0.95 (0.87-1.04)	0.60	1.03 (0.93-1.14)
Right stratum	4.54	0.97 (0.94-1.00)	0.88	1.00 (0.97-1.04)

* $p < .05$

CHAPTER 5:

Disruptions in white matter microstructure
associated with impaired visual associative
memory in chronic schizophrenia-spectrum
illness

Disruptions in white matter microstructure associated with impaired visual associative memory in chronic schizophrenia-spectrum illness

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Abstract

Background: Episodic memory ability relies on connectivity between the hippocampus and the prefrontal cortex. However, few studies have examined relationships between memory performance and white matter (WM) microstructure in hippocampal-prefrontal pathways in schizophrenia-spectrum disorder (SSD). Here, we investigated these relationships in individuals with first-episode psychosis (FEP) and chronic SSD using two distinct methodologies: (1) region-of-interest (ROI) tract-based analysis based on predefined white matter tracts involved in hippocampal-prefrontal connectivity, and (2) tractography analysis designed to interrogate the microstructure of white matter tracts in the hippocampal-prefrontal pathway.

Methods: Measures of white matter microstructure (fractional anisotropy [FA], radial diffusivity [RD], and axial diffusivity [AD]) were obtained for 47 individuals with chronic SSD, 28 FEP individuals, 52 older healthy controls, and 27 younger healthy controls. Following skeletonization with Tract-based Spatial Statistics (TBSS), mean values were extracted from four hippocampal-related ROIs (uncinate fasciculus, fornix, and dorsal and ventral cingulum bundle). Additionally, tractography analysis was performed between the hippocampus and four targets involved in hippocampal-prefrontal connectivity (thalamus, medial prefrontal cortex, amygdala, nucleus accumbens). Measures of white matter microstructure were then examined in relation to episodic memory performance (visuospatial associative memory and spatial memory) separately across each group.

Results: Both FEP individuals and those with chronic SSD demonstrated impaired episodic memory performance. However, abnormal white matter microstructure was only observed in individuals with chronic SSD. Reduced white matter microstructure in the fornix and the hippocampal-thalamic pathway in the right hemisphere was associated with poorer memory performance in individuals with chronic SSD.

Conclusions: These findings suggest that disruptions in white matter microstructure in the hippocampal-prefrontal pathway may contribute to memory impairments in individuals with chronic SSD but not FEP.

Introduction

Schizophrenia-spectrum disorder (SSD) is characterised by severe cognitive impairments, with deficits evident in both first-episode psychosis (FEP) and individuals with established illness (Aas et al., 2014; Bora et al., 2009). Although deficits occur across a range of cognitive domains, episodic memory is one of the most significantly impaired abilities in SSD (Heinrichs & Zakzanis 1998; Bora et al. 2009), even when factors such as duration of illness (Rushe et al. 1999), antipsychotic medication (Goldberg & Weinberger 1996), and level of psychotic symptoms (Aleman et al. 1999) are taken into account. Deficits in episodic memory ability are also associated with poorer psychosocial functioning (Velligan et al. 2000; Green et al. 2000; Sota & Heinrichs 2004; Juola et al. 2015; Nuechterlein et al. 2011; Barnett et al. 2005; Prouteau et al. 2005), and may be a predictor of transition to FEP in high risk individuals (Valli et al. 2012), suggesting that episodic memory ability may be an important treatment target to improve functional outcomes in individuals with SSD. Understanding the neural mechanisms underlying these deficits is critical in ameliorating episodic memory impairments in the disorder.

The critical role of the hippocampus for processing episodic memories is well-established (Burgess et al. 2002; Vargha-khadem et al. 1997; Smith & Mizumori 2006; Knierim 2015; Tulving 2002). In individuals with SSD, memory impairment has been associated with volume reductions in the hippocampus and its subfields (Hasan et al. 2011; Lappin et al. 2013; Nestor et al. 2007; Gur et al. 2000; Wannan et al. 2018), and with decreased activation of the hippocampus during memory-related tasks (Heckers et al. 1998; Ledoux et al. 2013; Weiss et al. 2003; Eyler Zorrilla et al. 2003), suggesting that disease-related abnormalities in the hippocampus may drive memory impairment in SSDs.

However, memory functioning is not dependent on the hippocampus alone, with evidence suggesting that connectivity between the hippocampus and the prefrontal cortex facilitates episodic memory performance (Jin & Maren 2015; Preston & Eichenbaum 2013; Sigurdsson & Duvarci 2016; Eichenbaum 2017). The hippocampal-prefrontal circuit comprises the major efferent anatomical connection from the hippocampal formation to the prefrontal cortex (Sigurdsson & Duvarci 2016; Godsil et al. 2013). While the hippocampus does connect directly to the prefrontal cortex by means of sparse projections onto the medial prefrontal cortex (mPFC), there are a number of intermediate brain regions that facilitate this connectivity (Godsil et al. 2013; Sigurdsson & Duvarci 2016). Specifically, regions including

the nucleus accumbens, thalamus, and the amygdala, receive input from the hippocampus and relay this to the prefrontal cortex. Plausibly, disruptions in connectivity between the hippocampus and any of these regions could result in memory impairment.

Hippocampal-prefrontal dysconnectivity has been proposed to be a core feature of psychiatric disorders such as SSD, and there is evidence to suggest that disruptions to this pathway may indicate vulnerability to psychosis (Godsil et al. 2013). Abnormal functional connectivity between the hippocampus and the prefrontal cortex has been observed not only in individuals with SSD (Ragland et al. 2004; Ragland et al. 2015; Meyer-Lindenberg et al. 2001; Meyer-Lindenberg et al. 2005; Glahn et al. 2005; Zhou et al. 2008), but also in their unaffected relatives (Rasetti et al. 2011; Schneider et al. 2017), and those at high risk of developing psychosis (Benetti et al. 2009), and has been associated with episodic memory impairment in the disorder (Ragland et al. 2004; Ragland et al. 2015; Zierhut et al. 2010). However, to date, evidence for disruptions to hippocampal-prefrontal connectivity in SSD are specific to functional connectivity, whereas no study has investigated anatomical or structural connectivity in relation to memory impairment in this population.

WM abnormalities have been observed in both FEP and chronic SSD (Di Biase et al. 2017; Kelly et al. 2017; Lee et al. 2013), and there is evidence that these abnormalities contribute to memory impairment in individuals with the disorder. Region of interest (ROI) and whole brain approaches have shown that poorer memory performance in chronic SSD is associated with increased mean diffusivity (MD) (Takei et al. 2008) and decreased fractional anisotropy (FA) (Nestor et al. 2007; Green et al. 2016) in the fornix, and decreased FA in the uncinate fasciculus (Kubicki et al. 2002); core regions associated with connectivity between the hippocampus and the prefrontal cortex. Impaired episodic memory performance has also been associated with FA reductions in the inferior frontal fasciculus and the inferior frontal occipital fasciculus (Liu et al. 2013), and with WM volume decreases in the orbitofrontal cortex and increases in the posterior parietal cortex (Green et al. 2016). However, the number of studies investigating the role of WM disruptions in memory impairment is currently small, and have focused exclusively on individuals with established SSD rather than those in early FEP and at-risk illness stages. Furthermore, there is a paucity of research utilising tractography analysis to interrogate WM connectivity between the hippocampus and the regions to which it is functionally connected as part of the hippocampal-prefrontal memory pathway.

The current study extended the findings of previous studies in two key ways. The first was the inclusion of two separate patient groups – those with first-episode psychosis (FEP) and those with chronic SSD – each with a respective healthy control group. The second was the use of two complementary WM approaches, including both ROI analysis based on predefined WM tracts, and tractography analysis designed to interrogate the microstructure of WM tracts in the hippocampal-prefrontal pathway. Thus, the aim of the current study was to examine relationships between episodic memory performance and measures of ROI- and tractography-based WM microstructure in FEP and chronic SSD. Such an approach would allow us to infer connections between the hippocampus and these key regions and determine whether abnormalities in this pathway are associated with memory impairment.

Methods

Participants

Forty-seven individuals with a chronic SSD (illness duration > 5 years) and 28 youth with FEP (< 2.5 years since first presentation to a mental health service for treatment of psychosis, number of psychotic episodes $\geq$ 1) were recruited as part of two separate studies. FEP were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC), Melbourne, Australia. EPPIC intake criteria include: first presentation of suspected psychotic illness, or less than six-months previous antipsychotic treatment for a first psychotic episode.

Individuals with chronic SSD were recruited from inpatient (20%) and outpatient (80%) clinics in Melbourne, Australia. All patients were diagnosed with a SSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 1994). Diagnoses were confirmed using either The Mini International Neuropsychiatric Interview (MINI; Sheehan *et al.*, 1998) or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First *et al.* 2002).

Two groups of age-matched healthy control participants with similar socioeconomic and educational backgrounds were recruited from the general community: young controls ($n = 27$; mean age of 21.95), and older controls ($n = 52$; mean age of 39.11). The MINI or the SCID were used to rule out current or past history of psychopathology in healthy controls.

Exclusion criteria for all participants were (1) a history of head injury or seizures, (2) diagnosis of a neurological disorder, (3) pregnancy, and (4) contraindication to MRI

scanning. Additional exclusion criteria specific to healthy controls included first-degree relatives with a history of psychotic illness.

The studies were approved by the Melbourne Health (2012.066, 2012.069) and Austin Health (H2012/04525) Human Research Ethics Committees and all participants provided written informed consent prior to participation.

Clinical measures

Negative symptoms in both patient cohorts were measured using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). Positive symptoms were measured using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) or the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). PANSS scores were converted to BPRS scores (Leucht et al. 2013), in order to provide measures of general psychopathology and positive symptoms that were comparable across both studies. All participants' functioning was evaluated using the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman, Skodol, & Lave, 1992). Current IQ was measured using the 2-subtest short form (Vocabulary and Matrix Reasoning) of the WAIS-III (Wechsler 1997). The Wechsler Test of Adult Reading (Wechsler 2001) was used to estimate premorbid IQ.

Neuropsychological assessment

Episodic learning and memory was assessed across all samples using the The Cambridge Neuropsychological Test Automated Battery (CANTAB) Paired Associates Learning (PAL) task (Cambridge Cognition 2016). Details of this task are described in *Chapter 2: General Methodology*.

Imaging data acquisition

Sixty diffusion-weighted volumes and 10 non-diffusion weighted (b0) volumes were obtained with an echo planar imaging sequence on a Siemens Avanto 3 T Magnetom TIM Trio scanner at the Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, VIC, Australia. Acquisition parameters were as follows: b-value = 3000s/mm², slice thickness = 2mm, image matrix = 104 x 104, in plane voxel resolution = 2 x 2 mm, field of view = 208 x 208, repetition time = 7750 ms, echo time = 112 ms, flip angle = 90°.

Image Processing

Diffusion-weighted imaging (DWI) data were pre-processed and registered to normalised stereotaxic space with the FMRIB Software Library (FSL; Jenkinson *et al.*, 2012). Pre-processing involved visual inspection for artifacts, during which six scans were removed from the analysis (1 control and 5 patients) due to poor image quality (cerebellar cropping and movement artifact) and another scan removed (1 patient), due to an incomplete imaging sequence. The remaining scans (sample population described in Table 1) underwent correction for motion and gradient-induced currents using affine registration to the first b0 image, and computation of FA, RD, and axial diffusivity (AD) volumes by fitting a tensor to the raw data using the FMRIB diffusion toolkit (FDT). Tract-based spatial statistics (TBSS) analysis of the diffusion-weighted data was then performed in the FSL software package according to the standard procedure (Smith *et al.* 2006). In brief, each subject's FA maps were first co-registered using non-linear registration (Andersson *et al.* 2007) to 1x1x1mm standard space, resulting in a standard space version of each individual FA image. Next, a study-specific thinned mean FA skeleton was generated to represent the centre of all WM FA voxels common to the group. The mean FA skeleton was thresholded at 0.2 to ensure that voxels containing grey matter and cerebrospinal fluid were excluded from analyses. Voxel values of each subject's FA map were projected onto the skeleton by searching the local maxima along the perpendicular direction from the skeleton.

ROI Analysis

Mean white matter measurements of FA, RD and AD were extracted for the bilateral fornix, and for the dorsal cingulum bundle, the ventral cingulum bundle and the uncinate fasciculus in the left and right hemisphere separately, resulting in 7 ROIs in total. Mean values from each ROI were extracted using a number of masks applied to the skeletonised TBSS data. A bilateral fornix mask, obtained using a novel template developed by Brown *et al.* (Brown *et al.* 2017), was used due to difficulties separating the structure over the midline of the brain. Left and right hemisphere masks for the dorsal and ventral cingulum bundles, and the uncinate fasciculus, were selected from the John Hopkins University (JHU) white matter tractography atlas (Wakana *et al.* 2004). ROI masks were restricted to the mean FA skeleton mask.

Tractography

Probabilistic tractography from the seed region (hippocampus) to the target regions (mPFC, thalamus, nucleus accumbens, amygdala) was performed using FSL's ProbtrackX program

(Behrens et al. 2007; Behrens et al. 2003). The hippocampus was extracted using MAgE T Brain software (Chakravarty et al. 2013; Pipitone et al. 2014: [//github.com/CobraLab/MAGeTbrain](https://github.com/CobraLab/MAGeTbrain)), as described previously (Wannan et al. 2018), and target regions were extracted using FSL's Harvard-Oxford probabilistic cortical and subcortical atlases, thresholded at 25%. Seed and target regions were non-linearly registered to each participant in the current study using the method described above. As hippocampal-prefrontal connections are largely ipsilateral, tractography was performed separately for each hemisphere, and the contralateral hemisphere was excluded from analyses using a mask. This resulted in 3 ipsilateral tracts in each hemisphere as tracts of interest (see Figure 1 for example tracts in a representative subject). Five thousand samples were initiated from each voxel in the seed region, with a step-length of 0.5mm, and fiber threshold of 0.01. Resulting pathways were normalised by dividing the number of streamlines passing through each voxel by the total number of generated streamlines (i.e., the *waytotal* value in FSL). This approach helps to ensure that results are not adversely impacted by differing mask sizes, tract sizes, or inclusion of voxels with a low probability of truly falling within a generated tract. The normalised pathways were then used to extract weighted mean FA, RD, and AD values, whereby voxels that had a higher probability of connection contributed more heavily towards the calculated mean value. Tractography successfully tracked pathways between the hippocampus and the amygdala, nucleus accumbens, and thalamus in both hemispheres. However, tractography between the hippocampus and mPFC did not produce reliable tracts, possibly reflecting the sparse physical connections between these two regions, and these analyses were therefore excluded from further interrogation.

Data Analysis

Analysis of demographic data

Group differences on demographic measures were examined using chi-square tests for categorical data, and t-tests for continuous variables. Three separate analyses were conducted: FEP vs younger controls, chronic vs older controls, FEP vs chronic.

Between-group differences in PAL performance

PAL trials were modelled using robust negative binomial regression due to the fact that data were positively skewed count data, and variances were greater than means in patient groups. Age and current IQ were included as covariates. Three separate analyses were conducted: FEP vs younger controls, chronic vs older controls, FEP vs chronic.

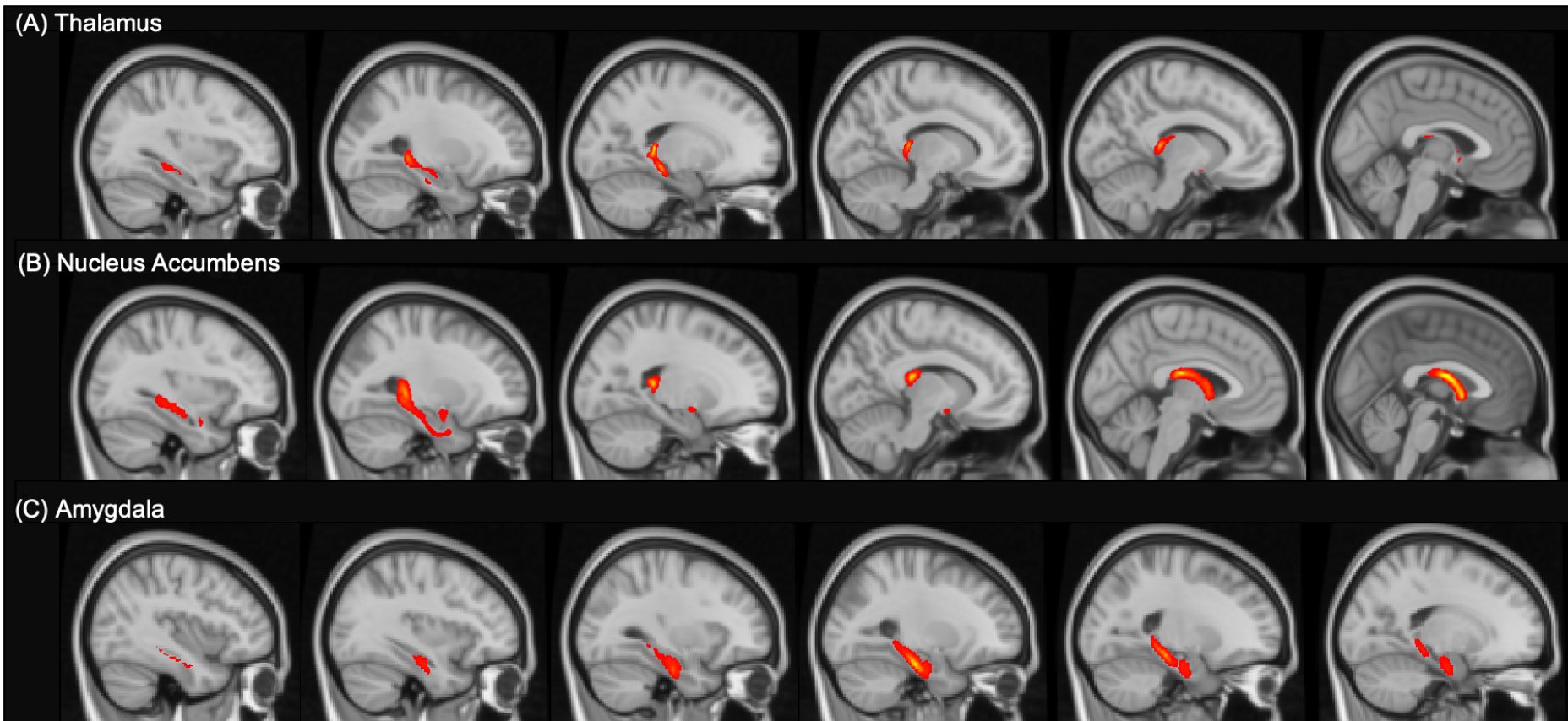


Figure 1. Hippocampal pathways of a representative subject. Saggital views show course of hippocampal connections with (A) thalamus, (B) nucleus accumbens, and (C) amygdala in the left hemisphere.

Between-group differences in white matter indices

Region of interest approach

Analysis of covariance (ANCOVA) was used to compare FA, RD, and AD of the ROIs between groups, with age included as a covariate. Three separate analyses were conducted: FEP vs younger controls, chronic vs older controls, FEP vs chronic. For ROI analyses, error control across the 21 independent tests (7 ROIs by 3 WM indices) was implemented using a False Discovery Rate of 5% for each between-group comparison. For tractography analyses, an FDR of 5% was applied across the 18 independent tests (6 tracts x 3 WM indices).

Relationships between white matter indices and memory performance

A series of robust generalized linear models (GLMs) were conducted to test for relationships between memory ability and WM indices separately in each group. For each model, memory performance (PAL trials) was included as the dependent variable and each WM index (across 7 ROIs or 6 tractography connections) as the independent variable, with age as a covariate. Error control was implemented using an FDR of 5% across 21 independent tests for the ROI analyses (7 ROIs x 3 WM indices) and across 18 independent tests for the tractography analyses (6 ipsilateral tracts x 3 WM indices).

Supplementary analyses

A number of supplementary analyses were carried out, including (1) comparison of whole-brain white matter microstructure between groups; (2) Whole-brain relationships between WM indices and PAL performance; (3) Correlations between antipsychotic medication dose and white matter indices, and; (4) Correlations between antipsychotic medication dose and PAL performance. Details of these analyses can be found in supplementary materials.

Results

Demographic results

Demographic data are displayed in Table 1. There were no group differences in age or sex for the two patient groups when compared to their respective healthy control groups. Both patient groups had significantly lower current IQ, premorbid IQ, years of education, and SOFAS scores compared to their respective healthy control groups. Individuals with chronic SSD also had significantly lower current IQ and SOFAS scores than FEP individuals, however there were no differences in premorbid IQ or years of education between patient groups. Although there were group differences in IQ, it is difficult to disentangle these effects

Table 1. Demographics

	Group				t-statistic/ χ^2		
	FEP	Younger HC	Chronic	Older HC	FEP vs. Younger HC	Chronic vs. Older HC	FEP vs. Chronic
Age	21.18 (1.98)	21.94 (2.00)	39.18 (10.59)	39.18 (10.59)	t = 1.43	t = 0.25	t = 10.03**
Gender (M/F)	21/7	17/10	30/17	34/18	$\chi^2 = 0.93$	$\chi^2 = 0.03$	$\chi^2 = 1.01$
Current IQ	94.89 (17.02)	119.19 (9.61)	86.57 (17.40)	114.26 (12.42)	t = 6.55**	t = 8.69**	t = 2.00
Premorbid IQ	98.00 (15.25)	112.15 (12.05)	92.05 (14.04)	106.87 (10.24)	t = 3.81**	t = 5.54**	t = 1.66
Years of education	12.33 (2.22)	15.009 (1.86)	12.80 (3.52)	15.64 (2.89)	t = 4.79**	t = 4.14**	t = 0.62
SOFAS	56.04 (10.11)	85.44 (6.93)	45.52 (14.91)	79.12 (11.43)	t = 12.54**	t = 12.47**	t = 12.17**
Illness duration (years)	1.83 (0.83) [#]	-	17.78 (8.23)	-	-	-	-
CPZ equivalent	421.48 (439.61)	-	989.21 (574.73)	-	-	-	t = 4.36**
Positive symptoms	12.74 (4.83)	-	16.23 (5.82)	-	-	-	t = 2.55*
Negative symptoms	25.00 (13.64)	-	42.36 (17.37)	-	-	-	t = 4.48**

* $p < .05$ ** $p < .01$ [#] For FEP patients, illness duration includes both duration of full-threshold and prodromal symptoms

Abbreviations: FEP, first-episode psychosis; HC, healthy control; SOFAS, Social and Occupational Functioning Assessment Scale; CPZ, chlorpromazine

from the disorder itself due to the intrinsic nature of IQ deficits to SSDs (Kahn & Keefe 2013).. Therefore, IQ was not included as a covariate in any of the regression models.

Neuropsychological results

As seen in Figure 2, FEP individuals were impaired on visual associative memory (Wald $\chi^2 = 3.40$, $p < .05$) relative to younger healthy controls. Individuals with chronic SSD had severe impairments on visual associative memory (Wald $\chi^2 = 22.24$, $p < .001$) relative to older healthy controls. They also performed significantly worse than FEP individuals on the visual associative memory task (Wald $\chi^2 = 6.46$, $p < .05$).

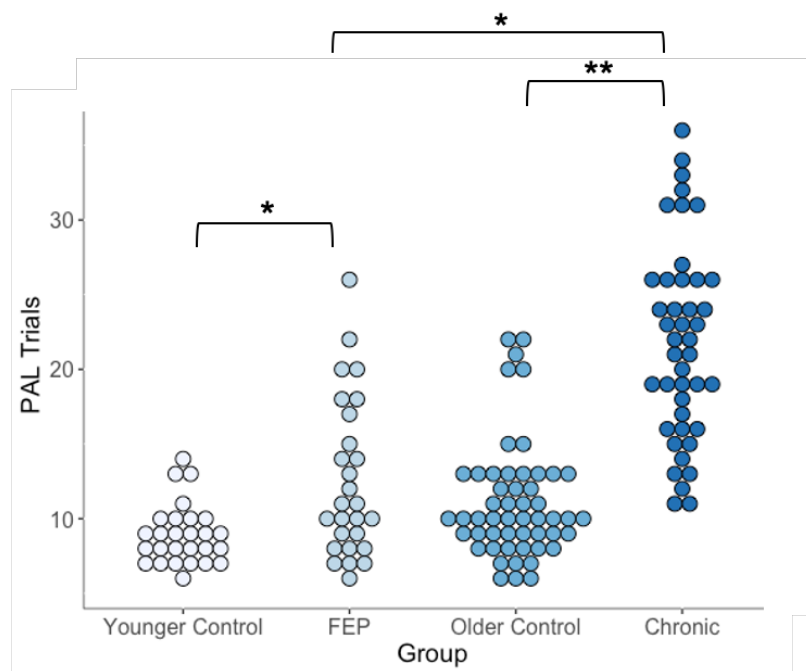


Figure 2. Number of trials required to complete the Paired Associates Learning task for younger healthy controls, first-episode psychosis (FEP) individuals, older healthy controls, and individuals with chronic schizophrenia. * = $p < .05$, ** = $p < .001$

Between-group differences in white matter indices

ROI analysis

As seen in Figure 3, FEP individuals showed no difference from younger healthy controls for FA, RD, or AD in any region. Conversely, individuals with chronic SSD had reduced FA and increased RD in the fornix, dorsal cingulum bundle, and uncinate fasciculus, and increased AD in the left fornix, compared to older healthy controls. Individuals with chronic SSD also had increased AD in the right UF relative to FEP individuals.

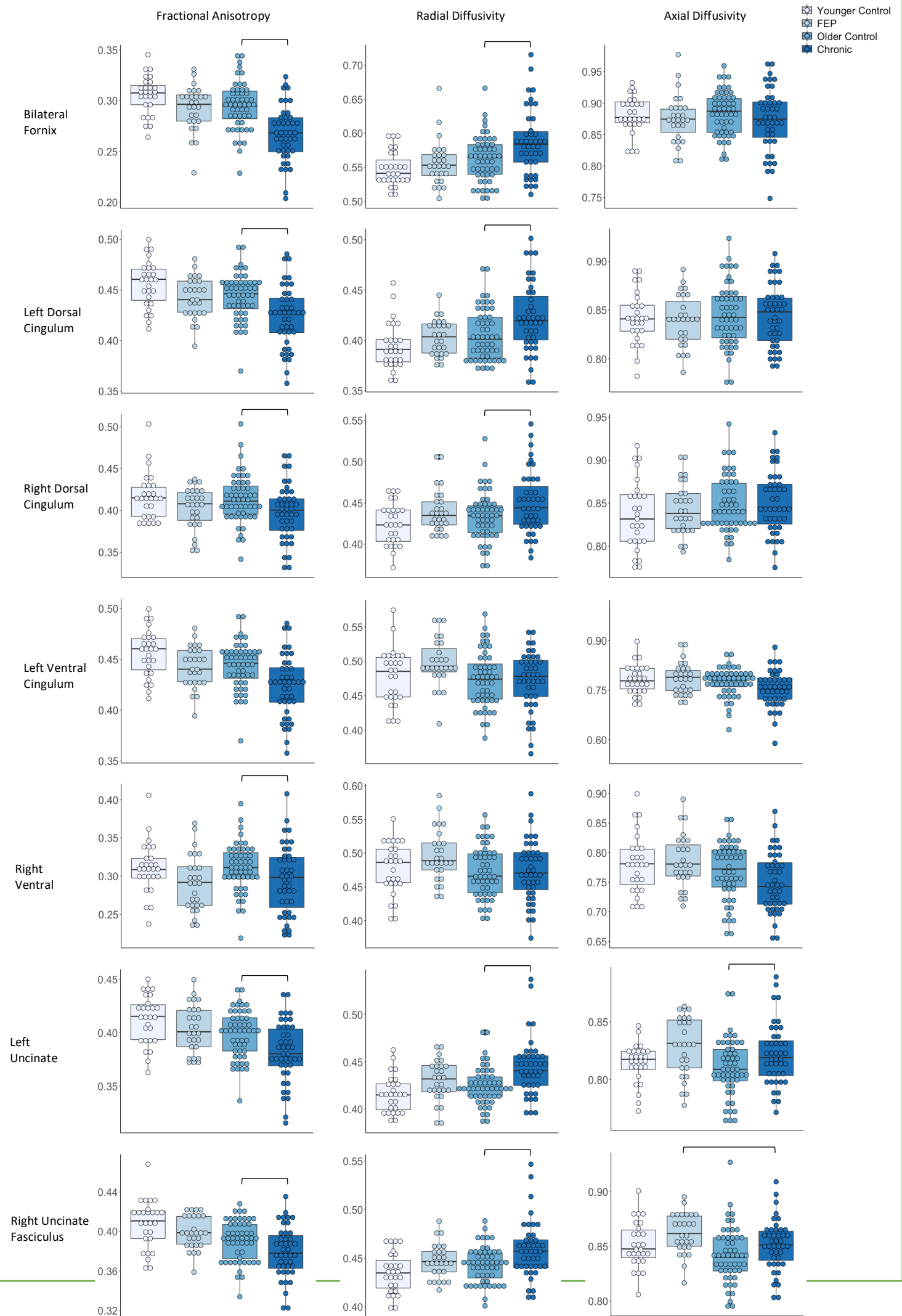


Figure 3. Mean values of fractional anisotropy, radial diffusivity (RD), and axial diffusivity (AD) for TBSS-derived regions of interest in younger healthy control, individuals with first-episode psychosis, older healthy controls, and individuals with chronic schizophrenia-spectrum disorder. RD and AD values are $\times 10^3$.

Tractography

As seen in Figure 4, FEP individuals showed no difference from younger healthy controls in any of the tracts of interest for FA, RD, or AD. In contrast, individuals with chronic SSD had reduced FA between the hippocampus and the right nucleus accumbens and the amygdala and thalamus bilaterally. They also had increased RD between the hippocampus and the amygdala and thalamus bilaterally, and increased AD between the hippocampus and the thalamus bilaterally.

Relationships between white matter indices and memory performance

ROI analysis

Significant relationships are displayed in Figure 5. Relationships between ROI white matter indices and memory performance were only observed in individuals with chronic SSD. In this group, poorer visual associative memory performance was associated with increased RD (Wald $\chi^2 = 8.25$, FDR-corrected $p < .05$) and AD (Wald $\chi^2 = 8.94$, FDR-corrected $p < .05$) in the fornix, and increased AD in the left dorsal cingulum bundle (Wald $\chi^2 = 7.24$, FDR-corrected $p < .05$).

Tractography

Significant relationships are displayed in Figure 6. In individuals with chronic SSD, poorer visual associative memory was associated with increased RD (Wald $\chi^2 = 12.05$, FDR-corrected $p < .05$) and AD (Wald $\chi^2 = 9.97$, FDR-corrected $p < .05$) between the hippocampus and the thalamus in the right hemisphere. In younger healthy controls, poorer visual associative memory was associated with reduced FA (Wald $\chi^2 = 14.68$, FDR-corrected $p < .05$) and increased RD (Wald $\chi^2 = 12.45$, FDR-corrected $p < .05$) between the hippocampus and the left thalamus. No relationships were observed in FEP individuals or older healthy controls.

Supplementary results

For full details, see supplementary information. Whole-brain voxel-wise analyses revealed that FEP individuals had reduced FA relative to younger healthy controls, predominantly in

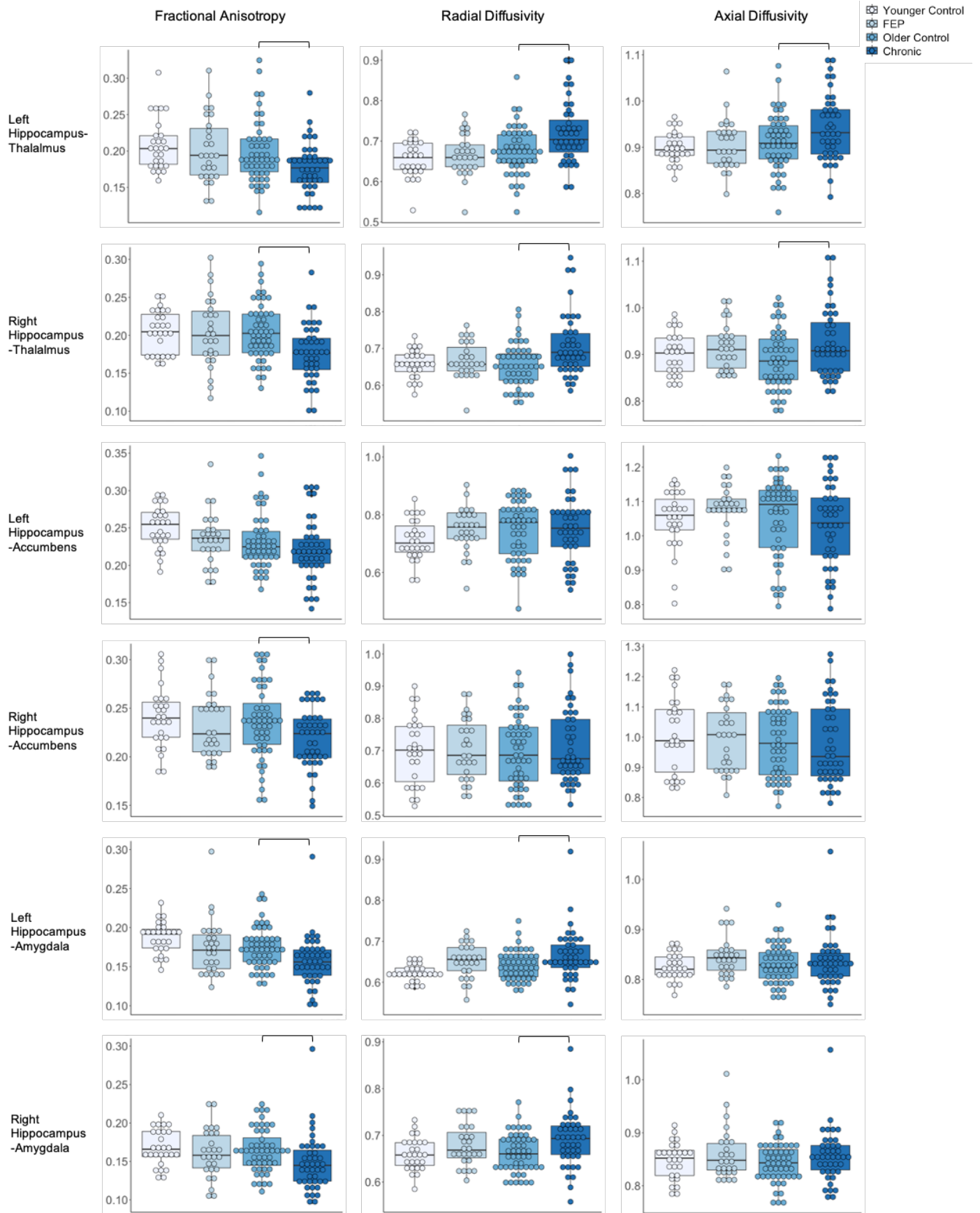


Figure 4. Mean values of fractional anisotropy, radial diffusivity (RD), and axial diffusivity (AD) for tractography-generated tracts in younger healthy control, individuals with first-episode psychosis, older healthy controls, and individuals with chronic schizophrenia-spectrum disorder. RD and AD values are $\times 10^3$.

the corpus callosum bilaterally. They also had increased RD across a number of regions, including the corpus callosum, anterior thalamic radiation, forceps major, UF, superior longitudinal fasciculus (SLF), and forceps minor, and the inferior fronto-occipital fasciculus (IFOF) bilaterally. In individuals with chronic SSD, widespread reductions in FA and increases in RD were observed relative to older healthy controls. A significant increase in AD was also observed in the right superior corona radiata. No relationships were observed between PAL performance and any whole-brain measure of white matter microstructure for any group.

Neither PAL performance nor white matter indices were correlated with antipsychotic medication dose.

Outliers were not found to influence white matter-PAL relationships.

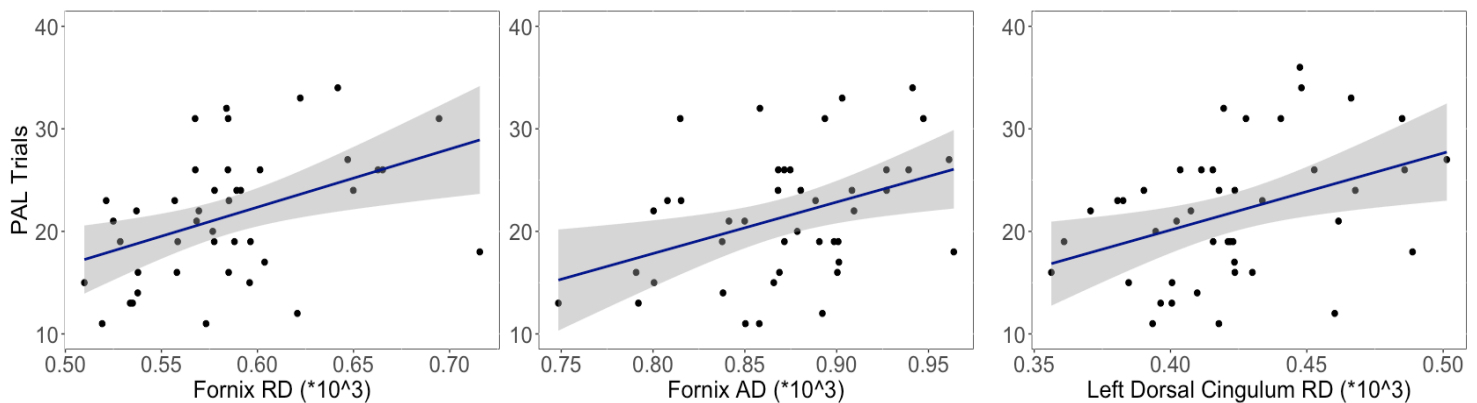


Figure 5. Relationships between region-of-interest white matter microstructure and number of trials required to complete the Paired Associated Learning task in individuals with chronic schizophrenia. RD = radial diffusivity; AD = axial diffusivity

Discussion

The aim of the current study was to extend our understanding of the neural basis of memory deficits in SSD by examining relationships between episodic memory performance and measures of ROI- and tractography-based white matter microstructure in FEP and chronic SSD.

Both FEP individuals and individuals with chronic SSD demonstrated impairments on an episodic memory task compared to their respective healthy control groups, although examination of effect sizes revealed that the magnitude of these impairments was substantially larger in the individuals with chronic SSD than the FEP individuals. When the

two patient groups were compared directly, individuals with chronic SSD demonstrated significant impairments on the PAL task compared to FEP individuals. These findings are consistent with previous studies revealing that individuals with chronic SSD have more severe impairments in visual episodic memory than those in early illness stages (Wood et al., 2002; Barnett et al., 2005; Stip et al., 2005; Donohoe et al., 2008).

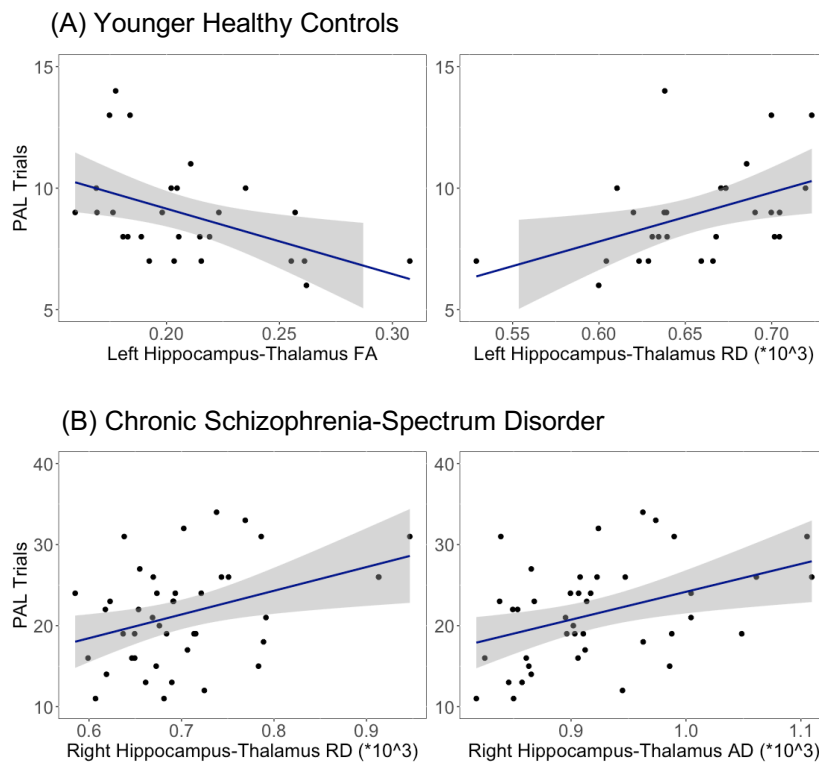


Figure 6. Relationships between tractography-derived white matter microstructure and number of trials required to complete the Paired Associated Learning task in (A) younger healthy controls, and (B) individuals with chronic schizophrenia-spectrum disorder. FA = fractional anisotropy; RD = radial diffusivity

In relation to white matter abnormalities, we observed widespread abnormalities in white matter microstructure in individuals with chronic SSD, regardless of the methodology used. The ROI analysis revealed that individuals with chronic SSD had reduced FA and increased RD in the fornix, dorsal cingulum, and uncinate fasciculus bilaterally. Additionally, tractography analysis found that individuals with chronic SSD had reduced FA and increased RD between the hippocampus and the amygdala and thalamus bilaterally, as well as increased AD between the hippocampus and thalamus bilaterally. These findings are consistent with numerous previous studies, which have identified widespread reductions in FA (Di Biase et al. 2019; Kelly et al. 2017; Klauser et al. 2017) and increases in RD (Hollaran et al. 2014; Seitz et al. 2016; Kelly et al. 2017) in individuals with SSD. Consistent with previous studies, (Pérez-Iglesias et al. 2010; Di Biase et al. 2017; Carletti et al. 2012; Lee et al. 2013; Zhou et al. 2017; Alvarado-Alanis et al. 2015; Cho et al. 2016; Von

Hohenberg et al. 2014; Rae et al. 2017), whole-brain analysis of white matter microstructure in FEP individuals also revealed reduced FA localised primarily to the corpus callosum, an increased RD across several key white matter tracts, including the corpus callosum, anterior thalamic radiation, forceps major, uncinate fasciculus, superior longitudinal fasciculus, forceps minor, and the IFOF bilaterally. However, despite these whole-brain abnormalities, neither the ROI nor tractography analyses revealed any abnormalities in the WM tracts of interest in the current study, suggesting that these may not be key sites of white matter pathology in our FEP sample – although this may be related to our small sample size and stringent correction for multiple comparisons.

Our findings in both FEP individuals and those with chronic SSD suggest that abnormalities in radial, rather than axial diffusivity may represent a key pathological marker in individuals with chronic SSD. Radial diffusivity is typically considered to be a measure of myelination (Song et al. 2002), whereas axial diffusivity measures axonal integrity or injury (Song et al. 2003). The current findings therefore suggest that white matter abnormalities in chronic SSD may be driven by demyelination rather than a reduction in axonal density. This is consistent with previous studies showing *in vivo* MRI-derived reductions in myelination, as measured by myelin water fraction, in both early and chronic SSD (Vanes et al. 2019; Flynn et al. 2003; Vanes et al. 2018; Lang et al. 2014), and with post-mortem studies showing reductions in the number of oligodendrocytes and their associated proteins in individuals with SSD (Vostrikov & Uranova 2011; Vostrikov et al. 2007; Flynn et al. 2003; Takahashi et al. 2011).

In the current study, the connectivity and microstructure of white matter was related to memory ability in individuals with chronic SSD and younger healthy controls. Specifically, analyses of select white matter tracts revealed that poorer visual associative memory was associated with increased RD and AD in the fornix, and with increased RD in the left dorsal cingulum bundle, in individuals with chronic SSD. Additionally, poorer visual associative memory was related to increased RD and AD between the hippocampus and the thalamus in the right hemisphere in individuals with chronic SSD. Poorer PAL performance was also associated with reduced FA and increased RD between the hippocampus and the thalamus in the left hemisphere in younger healthy controls. These findings suggest that abnormal white matter microstructure of the fornix, the cingulum bundle and in the pathway between the hippocampus and the thalamus is implicated in memory impairment in individuals with chronic SSD, when white matter abnormalities are evident in the illness.

Performance on paired associates learning tasks, similar to the one used in the current study, is dependent upon concurrent activation of the hippocampus and the prefrontal cortex (Eichenbaum 2017; Preston & Eichenbaum 2013; Simons & Spiers 2003), which is supported by the fornix. As the major output tract of the hippocampus, the fornix facilitates connectivity between the medial temporal lobe and several other brain regions, including the hypothalamus, anterior cingulate cortex, nucleus accumbens, striatum, medial prefrontal cortex, and septal regions (Parent et al. 2010; Douet & Chang 2015; Bubb et al. 2017). Given that the anatomical connections of the fornix form part of well-established memory networks, it is perhaps unsurprising that previous studies have identified relationships between white matter microstructure in the fornix and performance on tasks of episodic memory, not only in SSD (Green et al. 2016; Takei et al. 2008; Nestor et al. 2007), but also in healthy children, in younger and older adults (Douet et al. 2014; Zahr et al. 2009; Rudebeck et al. 2009; Metzler-Baddeley et al. 2011), and in Alzheimer's disease (Ringman et al. 2007; Zhuang et al. 2013). Our findings are thus consistent with previous studies yet extend upon them by demonstrating that abnormal axial diffusivity in the fornix is also associated with memory impairment in individuals with chronic SSD but not FEP individuals, and is the first to identify these relationships in a test of non-verbal episodic memory.

Observed relationships between hippocampal-thalamic white matter microstructure and memory performance in both individuals with chronic SSD and younger healthy controls are also consistent with the critical role of the thalamus, and in particular, the anterior and mediodorsal nuclei and the nucleus reuniens, in facilitating connectivity between the hippocampus and the mPFC (Zola-Morgan & Squire 1993; Dolleman-ven der Weel et al. 2019; Pergola & Suchan 2013; Aggleton et al. 2010). Connectivity between the hippocampus and the thalamus is considered critical for memory performance (Aggleton et al. 2010; Bubb et al. 2017; Dolleman-ven der Weel et al. 2019). It has been suggested that the thalamus supports memory and other cognitive processes through its role in shaping mental representations (Wolff & Vann 2019). Of note, one of the key pathways between the thalamus and mPFC is the cingulum bundle (Bubb et al. 2017), which was also associated with memory performance in individuals with chronic SSD in the current study. Together, these findings point to disruptions in key hippocampal-thalamic-prefrontal pathways as playing a critical role in memory impairment in SSD.

It is also interesting that, in individuals with chronic SSD, poorer memory performance was associated with increases in both radial *and* axial diffusivity – both in the fornix and in the

hippocampal-thalamic pathway. Myelin pathology is thought to be represented by *increases* in RD, however, axonal pathology is typically associated with *decreases* in AD, which measures the rate of diffusion along the principal axis of a fiber bundle (Budde et al. 2009; Song et al. 2003). Based on these conventions, we would expect to see poorer memory performance associated with reduced axial diffusivity. However, findings regarding AD in previous studies are far from consistent, and a number of studies have found increased AD to be associated with poorer behavioural outcomes and increased neurodegeneration across a range of diseases, in ageing individuals, and in those with traumatic brain injury (Newcombe et al. 2011; Della Nave et al. 2011; Mielke et al. 2012; Arfanakis et al. 2016; Mayo et al. 2019; Lancaster et al. 2016). One potential explanation for these findings is that cellular necrosis or reductions in axonal density in these regions may lead to encroachment of cerebrospinal fluid, resulting in less restricted diffusion both radially and axially. Alternatively, increased axial diffusivity may reflect changes in the dominant cell type contributing to the diffusion signal – for example, increased numbers of microglia or astrocytes replacing axonal bundles, leading to increased diffusion in all directions (Newcombe et al. 2011). Without complementary assays (for example, histology) it is not possible to determine the exact mechanisms underlying increased axial diffusivity in the current study. However, it is clear that they are related to pathological processes that are occurring only in the most chronically ill patients, and not in those experiencing FEP.

Limitations and future directions

Our findings should be considered in the context of several limitations. Firstly, it is difficult to tease out potential medication effects in the current study as cumulative medication exposure was not measured. The effects of medication on white matter diffusion properties remain unclear, with various studies finding increases (Reis Marques et al. 2014), decreases (Wang et al. 2013; Szeszko et al. 2014), and no change (Zeng et al. 2016) in FA in relation to commencing antipsychotic treatment. In the current study, chlorpromazine equivalent medication dosage was not associated with either white matter microstructure or memory ability, however it was not possible to determine whether there may be effects of cumulative medication use on white matter microstructure. It is also difficult to rule out partial volume effects from our findings, particularly in regions such as the fornix, which can be prone to such effects due to proximity to the lateral ventricles. However, our diffusion weighted scans were acquired with high b-values (3000s/mm²), and a study-specific white matter skeleton was used in TBSS, which has been shown to minimize partial volume effects compared to the use of the standard FMRIB skeleton (Bach et al. 2014). Finally, it is important to note that

duration of illness for our FEP sample included both duration of prodromal and full-threshold symptoms, and that this group consisted of only a small number of participants, reducing statistical power in this sample.

Conclusion

In summary, we found that while both FEP individuals and those with chronic SSD demonstrated impaired episodic memory performance, reduced white matter microstructure in key memory-related tracts was only observed in individuals with chronic SSD, with such alterations relating to individual variation in episodic memory performance in key tracts. Specifically, reduced white matter microstructure in the fornix and hippocampal-thalamic pathway in the right hemisphere was associated with poorer memory performance in individuals with chronic SSD, with such relationships absent in individuals with FEP. These findings suggest that disruptions in connectivity between the hippocampus and subcortical regions implicated in the hippocampal-prefrontal pathway may contribute to memory impairments in individuals with chronic illness. Longitudinal studies with larger samples of FEP individuals would help to elucidate whether these white matter-memory relationships strengthen over time following psychosis onset, or whether they might be present in certain subsets of participants at the time of the first psychotic episode.

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Disruptions in white matter microstructure associated with impaired visual associative memory in schizophrenia-spectrum illness

Supplementary Information

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Methods

Data Analysis

Whole-brain white matter microstructure

Voxel-wise comparisons of whole-brain FA, RD, and AD between groups were carried out with the FSL Randomise software (Nichols & Holmes 2003), using the Threshold-Free Cluster Enhancement method, a nonparametric cluster-size-based procedure (Friston et al. 1994; Smith & Nichols 2009). This approach was undertaken in order to determine whether any group differences or relationships with memory performance might exist for white matter tracts outside of the specified ROIs. Age was included as a covariate in each analysis. A family-wise error corrected p value was calculated for each cluster (5000 permutations). Due to the number of white matter indices (FA, RD, AD) and comparisons (FEP vs younger controls, chronic vs older controls, FEP vs chronic), corrected $p < .008$ values were considered significant (3 white matter indices X 2 contrasts).

Whole-brain relationships between WM indices and PAL performance

Relationships between memory performance and whole brain measures of FA, RD, and AD were also analysed with FSL's Randomise software (Nichols & Holmes 2003), using the methods described above and covarying for age. Corrected $p < .008$ values were considered significant (3 white matter indices X 2 contrasts).

Correlations between antipsychotic medication dose and white matter indices and PAL performance

In order to examine relationships between antipsychotic medication dosage and measures of white matter microstructure, a series of Pearson's correlations were carried out between CPZ equivalent antipsychotic dose and mean FA, RD, and AD in each ROI and tractography-generated tract in both FEP individuals and those with chronic SSD. Results were corrected for multiple comparisons in the manner described above.

Relationships between CPZ equivalent antipsychotic dose and PAL performance were examined in FEP individuals and those with chronic SSD using robust generalized linear models, with age included as a covariate.

Results

Whole-brain white matter microstructure

As seen in Supplementary Figure 1, FEP individuals had reduced FA relative to younger healthy controls, predominantly in the corpus callosum bilaterally, and extending into the right posterior thalamic radiation, and the posterior corona radiata. They also had increased RD across a number of regions, including the corpus callosum, anterior thalamic radiation, forceps major, UF, superior longitudinal fasciculus (SLF), and forceps minor, and the inferior fronto-occipital fasciculus (IFOF) bilaterally. No differences in AD were observed between FEP individuals and younger healthy controls. As seen in Supplementary Figure 2, widespread reductions in FA and increases in RD were observed in individuals with chronic SSD relative to older healthy controls in the inferior longitudinal fasciculus, corpus callosum, inferior frontal fasciculus, IFOF, SLF, anterior thalamic radiation, forceps minor, corona radiata, corticospinal tract, and fornix crescent bilaterally. A significant increase in AD was also observed in the right superior corona radiata. There were no differences between FEP individuals and individuals with chronic SSD on any whole-brain WM measure.

No relationships were observed between PAL performance and any measure of white matter microstructure for any group.

Correlations between antipsychotic medication dose and white matter indices and PAL performance

Of the 39 correlations in each patient group (3 WM indices X 13 ROIs and tractography-generated tracts), significant relationships were only observed between CPZ equivalent dosage and RD ($r = -0.33, p = .025$) and AD ($r = -0.32, p = .029$) in the right hippocampal-nucleus accumbens pathway in individuals with chronic SSD. However, these relationships did not survive correction for multiple comparisons.

PAL performance was not associated with CPZ equivalent dose in either FEP individuals (Wald $\chi^2 = 0.34, p = .562$) or those with chronic SSD (Wald $\chi^2 = 2.22, p = .137$).

Ensuring validity of white matter-memory relationships

In order to ensure that these findings were not influenced by outliers, all significant analyses were re-run with any potential outliers (values lying more than 1.5 steps outside the first and third quartiles) replaced with the next highest or lowest value. With these adjustments, all relationships remained highly significant and results remained unchanged.

CHAPTER 6:

General Discussion

6.1. Thesis overview and summary of results

In this thesis, we have combined cognitive and neuroimaging data in individuals with first-episode and chronic psychosis in order to evaluate three primary aims:

- 1. To investigate the longitudinal course of episodic memory ability over a 5-11 year follow-up period in individuals with first-episode psychosis.**
- 2. To investigate relationships between visual associative memory performance and hippocampal subfield volumes in FEP individuals and individuals with chronic schizophrenia-spectrum disorders.**
- 3. to investigate whether visuospatial associative memory ability is related to white matter microstructure in the hippocampal-prefrontal pathway in FEP individuals and individuals with chronic schizophrenia-spectrum disorders.**

First, to explore the longitudinal course of memory ability following psychosis onset, the CANTAB Paired-Associates Learning task and a verbal memory task was administered to individuals with first-episode psychosis (FEP) at two time-points: baseline and 5-11 years post psychosis onset. This FEP group had an extremely short duration of illness at baseline – 0.3 years on average – making them an ideal sample in which to identify cognitive change that may occur in the period immediately following psychosis onset. Second, as it was unclear whether volume reductions in particular hippocampal subfields were related to memory impairments in FEP individuals and individuals with chronic schizophrenia-spectrum disorders, the relationships between hippocampal subfield volumes and visuospatial associative memory across various stages of psychosis were examined. Further, while a number of studies had investigated relationships between hippocampal volumes and memory performance in individuals with psychosis, few had examined relationships between memory performance and measures of white matter integrity. Therefore, in order to address the third aim of this thesis, we examined relationships between visuospatial associative memory and various measures of white matter microstructure in a number of hippocampal-prefrontal white matter tracts across stages of schizophrenia-spectrum disorders.

Several key findings emerged in addressing our key study questions. In *Study 1 (longitudinal)*, we reported that, while no impairment in visuospatial associative memory or verbal memory was present at baseline in FEP individuals relative to healthy control

individuals, there was a significant deterioration in visuospatial associative memory ability over the follow up period. In contrast, change in verbal associative memory did not differ between patients and HCs, with both groups showing improved ability over time.

In *Study 2 (cross-sectional)*, we found that both FEP individuals and individuals with a chronic schizophrenia-spectrum disorder demonstrated impaired visuospatial associative memory compared to age-matched healthy control individuals, although the degree of impairment was greater in individuals with a chronic schizophrenia-spectrum disorder. Smaller hippocampal subfield volumes were only observed in individuals with a chronic schizophrenia-spectrum disorder relative to controls. Finally, in both FEP individuals and individuals with a chronic schizophrenia-spectrum disorder, relationships between visuospatial associative memory ability and hippocampal subfield volumes were observed that were not present in healthy control subjects, suggesting that smaller hippocampal subfield volumes were associated with poorer visuospatial associative memory in both early and late illness stages. The subfields that were implicated in both patient groups included the CA4/dentate gyrus (CA4/DG), and the stratum radiatum/lacunosum /moleculare (SRLM).

Finally, in *Study 3 (cross-sectional)* white matter microstructure abnormalities in key hippocampal-prefrontal white matter tracts were present only in individuals with a chronic schizophrenia-spectrum disorder, with FEP individuals showing no differences from younger healthy controls. In individuals with a chronic schizophrenia-spectrum disorder, we also observed relationships between visuospatial associative memory impairment and white matter microstructure abnormalities in the fornix and cingulum bundle, as well as in the hippocampal-thalamic pathway. These relationships included reduced fractional anisotropy (FA) and increased radial diffusivity (RD) and axial diffusivity (AD) in relation to poorer memory performance. These relationships were not present in FEP individuals or older healthy controls, however, white matter microstructure in the hippocampal-thalamic pathway was associated with memory performance in younger healthy controls. In these individuals, reduced FA and increased RD was associated with poorer memory performance.

6.2. Trajectory of episodic memory performance following a first psychotic episode

The first aim of this thesis was to map the trajectories of visual and verbal associative memory following a first psychotic episode. While the dominant notion of cognitive

impairment in schizophrenia-spectrum disorders is currently that, for most, significant impairments are present at the time of illness onset, with little change over the course of the illness (Barder et al., 2013; Bora & Murray, 2013; Bozikas & Andreou, 2011), the results of our current studies suggest that visual associative memory ability is preserved at the time of illness onset, but appears to deteriorate as the illness progresses. In *Study 1*, we revealed that individuals with FEP had preserved visual associative memory at the time of illness onset, with deterioration of this ability observed over a 5-11-year follow-up period. These findings extend on previous cross-sectional studies, which have found this ability to be preserved in individuals with FEP (Barnett et al., 2005; S. J. Wood et al., 2002), but substantially impaired in chronic schizophrenia-spectrum disorders (Donohoe et al., 2008; Stip et al., 2005; S. J. Wood et al., 2002), by confirming that illness-stage-dependent differences observed in individuals with FEP and chronic schizophrenia-spectrum disorders are due to *deterioration* of this ability over time.

Interestingly, the FEP individuals who participated in our cross-sectional studies (*Chapters 4 and 5*) did show deficits on the PAL task relative to the younger healthy control group, despite having almost identical mean IQ scores and years of education. However, it is worth noting that these impairments were relatively mild, and driven largely by a sub-group of poorly performing individuals. Individuals with chronic schizophrenia-spectrum disorders, on the other hand, showed severe impairments relative to older healthy controls, and also performed more poorly than FEP individuals. Given the longer illness duration of FEP individuals in the cross-sectional studies (on average 1.83 years, although this includes duration of prodromal symptoms) compared to the longitudinal study (0.3 years), it is possible that some deterioration had already taken place in the former group. If this is the case, it would suggest the window in which to prevent cognitive deterioration following the onset of FEP may be quite short, and that interventions targeting the prodromal stage of the illness may be more beneficial in this respect.

Declines in visual associative memory ability identified in the current study can be contrasted against stable deficits in pattern recognition (*Study 1*) and spatial working memory (see unpublished data, Appendix 1) observed in these same individuals over the follow-up period. This dissociation in the trajectories of different cognitive abilities following psychosis onset is somewhat consistent with a recent long-term follow-up studies of FEP individuals, in which verbal memory ability was found to deteriorate while other abilities, including working

memory, processing speed, and verbal fluency, were found to be stably impaired (Zanelli et al., 2019). Unfortunately, Zanelli et al. (2019) did not include a measure of visual associative memory, and we are therefore unable to directly compare our findings. However, in contrast to the findings of Zanelli et al (2019), as well as other recent longitudinal studies (Fett et al., 2020; Rodríguez-Sánchez et al., 2013), we observed improvement in verbal memory ability over the follow-up period in both FEP individuals and healthy control subjects. This is in direct contrast to Fett et al. (2020) who observed deterioration on the same task used in our study over an 18-year follow-up period. Together, our findings and those of other longitudinal studies highlight two important points in regards to longitudinal studies in individuals with FEP, or with schizophrenia-spectrum illness in general. The first is that it is likely that cognitive deterioration in schizophrenia-spectrum disorders is not a generalised phenomenon, but rather specific to certain cognitive domains, at least in the decade following illness onset. Long-term follow-up studies that have observed cognitive deterioration following FEP onset have not observed this deterioration across all cognitive domains, though the number of implicated areas of functioning does appear to increase with increasing follow-up duration (Fett et al., 2020; Rodríguez-Sánchez et al., 2013; Zanelli et al., 2019).

The second issue worth considering is that two timepoints (i.e. baseline and follow-up) may not be sufficient to truly understand when and how cognitive changes occur in individuals with schizophrenia-spectrum disorders, particularly when the follow-up duration is long. For example, it is possible that verbal associative memory ability improves in line with healthy individuals in the period immediately following FEP onset, with deterioration occurring much later in the illness. This late deterioration could be associated with putatively accelerated brain ageing observed in the disorder (Cropley et al., 2017; Kochunov et al., 2013; Schnack et al., 2016; Van Rheezen et al., 2020), such that normal declines in episodic memory performance are occurring earlier in individuals with schizophrenia-spectrum illness than in healthy individuals. Accelerated brain ageing could also explain why the number of cognitive domains found to have deteriorated in Fett et al.'s (2020) study was greater than Zanelli et al.'s (2019) study and our own: the age at follow-up in the former study is approximately 10 years older. However, without multiple timepoints, it is impossible to truly interrogate this hypothesis.

What factors may underlie the cognitive trajectory after FEP?

Previous authors have suggested that domain-dependent differences in cognitive trajectories in individuals with schizophrenia-spectrum disorders may relate to a differential impact of the disorder on fluid versus crystallised cognitive abilities, with deterioration occurring only in areas of crystallised ability (Zanelli et al., 2019). However, this hypothesis is not consistent with the findings of Fett et al. (2020), who observed stability or improvement in areas of crystallised ability, such as verbal knowledge, and decline across a number of areas of fluid intelligence, including executive functions and processing speed. Furthermore, it is not consistent with their own findings in relation to deterioration of verbal memory ability, which is more closely linked to fluid abilities than crystallised (Schaie & Willis, 1993). Furthermore, this hypothesis cannot explain why some areas of functioning, such as visual associative memory, may be preserved at the time of FEP onset. In order to account for these findings, we have hypothesised that these differing trajectories may result from an interaction between the age of illness onset and stage of brain development (C Pantelis, Yucel, et al., 2009; Christos Pantelis et al., 2015). My findings in *Study 1* emphasise that, in order to understand the trajectories of different cognitive abilities in schizophrenia-spectrum disorders, it is essential to consider them in the context of typical brain and cognitive development from childhood through to adolescence and early adulthood.

The importance of considering typical brain maturation

The period from adolescence to early adulthood is characterised by a profound reorganization of cortical networks, facilitated by a number of processes, including synaptic pruning, myelin synthesis, and the refinement of neurotransmitter systems (Arain et al., 2013; Spear, 2013). Throughout this period, studies have identified longitudinal reductions in grey matter volumes, and white matter volumes have been shown to increase up until the third decade of life (Gogtay et al., 2011; Pfefferbaum et al., 1994; Sowell et al., 2003). It has been suggested that the rapid neurodevelopment occurring during adolescence leaves the brain vulnerable to insult, thus increasing the risk for mental disorders during this period (Paus et al., 2008). The brain regions that undergo the most substantial structural and functional change during adolescence and early adulthood, such as the frontal and temporal lobes, are those responsible for higher-order brain functions, including cognition and emotion regulation, and the perception and evaluation of risk and reward (Steinberg, 2005). Thus, cognitive development continues throughout adolescence and into early adulthood, with higher-order abilities, including executive function, working memory, and verbal skills, being refined during this period (Paus, 2005). Given that most individuals who develop a psychotic disorder

experience their first episode before the age of 25, it would appear as though psychosis tends to emerge during or at the end of a period of peak brain maturation (Gogtay et al., 2004, 2011; Moises et al., 2002).

Towards a brain maturation model for cognition

The findings from *Study 1* emphasise the importance of taking into account normal maturational trajectories and the typical age of onset of psychotic disorders when interpreting domain-specific cognitive trajectories following a FEP. From the basis of *Study 1*, as well as other unpublished data from our group (see Appendix 1), we propose that cognitive functions that are maturing around the time of illness onset, or that continue to develop into adulthood, will be those that are maximally impacted in individuals with psychotic disorders.

Conversely, areas of cognition that develop earlier in life, prior to the onset of psychosis, are more likely to be preserved at the time of illness onset. Deterioration of these preserved abilities, as seen in *Study 1*, may occur as a result of the neuroprogressive processes that have been observed in the disorder, which affect both grey and white matter (Cali F

Bartholomeusz et al., 2016; Cropley et al., 2017; Fusar-poli et al., 2013; Olabi et al., 2011).

Two areas of functioning that appear to be preserved at illness onset are visual associative memory and attentional set-shifting. As with visual associative memory, previous studies have also consistently found evidence for severe impairments in set-shifting ability in individuals with chronic schizophrenia-spectrum disorders, using the CANTAB extra dimensional set shift (IED) task (Ceaser et al., 2008; Elliott et al., 1995; Jazbec et al., 2007; C Pantelis et al., 1999). However, in FEP individuals and those at high-risk for psychosis, this ability appears to be preserved or only minimally affected (Bartok et al., 2005; Hilti et al., 2010; Hutton et al., 1998; Leeson et al., 2009; C Pantelis, Wood, et al., 2009). These cross-sectional findings, which are suggestive of deterioration of set-shifting ability over the course of psychotic illness, are supported by our own unpublished longitudinal data in the same sample used in *Study 1*, which showed a decline in IED performance following a first psychotic episode (see Appendix 1). Interestingly, maximal performance on both visual associative memory and set-shifting tasks is already achieved by the time of puberty, with little improvement seen after eight years of age for attentional set-shifting (De Luca et al., 2003), and 11 years of age for associative memory (Thaler et al., 2013). Therefore, it is likely that these abilities have already finished maturing prior to the onset of psychotic illness, resulting in preserved functioning in early illness stages. Later deterioration of these abilities

may be related to progressive abnormalities in the brain regions or networks that are typically associated with these particular areas of functioning.

In contrast to visual associative memory and attentional set-shifting, one example of a cognitive function that may have its development disrupted by psychosis onset is spatial working memory ability, which is impaired prior to the onset of psychotic illness (S. J. Wood et al., 2003). A similar degree of spatial working memory impairment is observed in FEP individuals and individuals with chronic schizophrenia-spectrum disorders (C Pantelis, Yucel, et al., 2009; S. J. Wood et al., 2002), and deficits are stable over time (see unpublished data, Appendix 1). In healthy people, spatial working memory ability continues to develop into adulthood, with maximal performance achieved by the mid 20's (De Luca et al., 2003). In individuals with schizophrenia-spectrum disorders, however, it would appear as though the onset of the disorder leads to an *arrest* of normal development, resulting in a stable SWM impairment from the earliest stages of the illness. Thus, my findings from *Study 1*, together with the above unpublished findings in the same cohort, identify different cognitive trajectories (i.e. decline and arrest) occurring in early psychosis, as depicted in section 1.3.2 in Chapter 1. My thesis expands on this model by arguing the necessity to take into account both neurodevelopmental and neuroprogressive factors, and their interactions, when examining longitudinal cognitive trajectories in schizophrenia-spectrum disorders.

As discussed in *Study 1*, we failed to observe the expected decline in verbal associative memory ability in our sample of FEP individuals, and instead found a preservation of functioning relative to healthy controls, and improvement in scores over the follow-up period for both FEP individuals and healthy controls. Preservation of functioning on the verbal paired associates task observed in the current study is contrasted against a number of studies observing deficits on this task in FEP individuals (de Azua et al., 2013; Lindsberg et al., 2009; Matsui et al., 2007). One consideration here is that our study covaried for current IQ, whereas other previous studies did not. It is therefore possible that the VPA task is sensitive to the effects of generalised cognitive impairment, and controlling for IQ has therefore masked these deficits in our study. Indeed, verbal memory ability is also heavily influenced by a number of other cognitive processes, including verbal knowledge (Jordan et al., 2013), which is considered to be a crystallized cognitive ability and thus possibly less impacted by the illness (Van Rheenen et al., 2020). One of the benefits of the CANTAB PAL task in this

respect is that the test stimuli are not easily verbalised, meaning that the results are less likely to be confounded by verbal ability (S. J. Wood et al., 2002).

6.3. The neural correlates of psychosis-related memory impairment

Having established that visual associative memory ability shows a trajectory of decline following psychosis onset, we next sought to understand the neurobiological underpinnings of impairments in this particular area of functioning. Given the critical role of the hippocampus for memory ability, we chose to focus on this region across two separate structural neuroimaging studies utilising different imaging modalities: measurement of hippocampal subfield volumes from T1-weighted MRI volumes, and analysis of hippocampal connectivity using diffusion-weighted scans. The use of two different imaging methodologies allowed us to interrogate the role of the hippocampus in psychosis-related memory impairment in two different ways. The first was to identify whether particular subregions *within* the hippocampus were more strongly associated with memory impairment. The second placed the hippocampus within a broader brain connectivity framework, to determine whether disrupted connectivity *from* the hippocampus to other regions within the hippocampal-prefrontal memory network is implicated in memory impairments across illness stages. The latter approach is important given the increasing acceptance of the disconnection hypothesis of schizophrenia-spectrum disorders, which posits that the symptoms of schizophrenia-spectrum disorders, including cognitive symptoms, are related to disrupted brain connectivity (K. Friston et al., 2016; K. J. Friston & Frith, 1995; Weinberger, 1993).

6.3.1. Brain abnormalities in key memory-related brain regions in FEP individuals and individuals with chronic schizophrenia-spectrum disorders

6.3.1.1. Hippocampal subfield volumes

The study presented in *Study 2* aimed to investigate whether impairments in visual associative memory ability were related to volume reductions in particular hippocampal subfields across stages of schizophrenia-spectrum disorders. Identifying the particular hippocampal subfields that are implicated in schizophrenia-spectrum disorders may provide us with a better understanding of the mechanisms underlying hippocampal abnormalities in the disorder, and their behavioural manifestations. Consistent with our hypothesis, we identified widespread reductions in hippocampal subfield volumes in individuals with chronic schizophrenia-spectrum disorders, including the bilateral CA4DG, CA2CA3, and

SRLM, and the right subiculum, relative to older healthy controls. Though studies investigating hippocampal subfield volumes in schizophrenia-spectrum disorders are currently sparse, our findings are consistent with a handful of previous studies which identified reduced volumes across most examined hippocampal subfields in chronic schizophrenia-spectrum disorders (Haukvik et al., 2015; N. F. Ho et al., 2016; Mathew et al., 2014). Interestingly, in our recent-onset sample, we failed to detect any reductions in hippocampal subfield volumes relative to the younger healthy control group. This is contrary to recent studies in which individuals with first-episode or recent-onset psychosis were shown to have volume reductions across several hippocampal subfields, including the bilateral CA1 and CA4, and the left CA3 (Baglivo et al., 2018), the CA1, CA4, granule cell layer, subiculum, and presubiculum (Briend et al., 2020), or the CA4/DG (Kawano et al., 2015). However, another recent study of 90 minimally treated or antipsychotic-naïve patients with first-episode psychosis also failed to detect any reductions in hippocampal subfield volumes relative to healthy control subjects (Luckhoff et al., 2020). Taken together, the findings suggest that hippocampal abnormalities across the schizophrenia-spectrum are heterogeneous, particularly in the early stages of the disorder.

It has been proposed that pathology in the dentate gyrus might drive abnormalities in downstream hippocampal subfields in individuals with chronic schizophrenia-spectrum disorders (Tamminga et al., 2010). Consistent with this hypothesis, in *Study 2* the degree of volume loss in the dentate gyrus in individuals with chronic schizophrenia-spectrum disorders was of greater magnitude than that observed in other subfields, and this was the only region that came close to showing significant volume reductions in FEP individuals (i.e. uncorrected $p = .058$ in the left hemisphere). Worth noting is that previous longitudinal studies in FEP individuals have identified progressive volume loss in the CA4DG following psychosis onset (Kawano et al., 2015; W. Li et al., 2018; Rhindress et al., 2017). Together, these findings point to the dentate gyrus as a key site of pathology within the hippocampal formation in schizophrenia-spectrum illness, and it is possible that this dentate gyrus pathology is driving the abnormalities that were observed in the CA2CA3 and SRLM layers. Of note, subfields that are further downstream in the network (i.e. the CA1 and the subiculum) were unaffected. Future longitudinal studies would be well placed to examine whether hippocampal pathology may ‘spread’ throughout the subfields as psychotic illness progresses.

6.3.1.2. White matter

Consistent with our hypothesis, we observed widespread white matter microstructure abnormalities in individuals with chronic schizophrenia-spectrum disorders, both at a whole-brain level and when examining specific regions-of-interest (ROIs) and tractography-generated tracts. The ROI analysis revealed that individuals with chronic schizophrenia-spectrum disorders had reduced FA and increased RD in the fornix, dorsal cingulum, and uncinate fasciculus (UF) bilaterally. Additionally, tractography analysis found that individuals with chronic schizophrenia-spectrum disorders had reduced FA and increased RD between the hippocampus and the amygdala and thalamus bilaterally, as well as increased AD between the hippocampus and thalamus bilaterally. These findings are consistent with numerous previous studies, which have identified widespread reductions in FA (Maria Angelique Di Biase et al., 2019; Kelly et al., 2017; Klauser et al., 2017) and increased RD (Holleran et al., 2014; Kelly et al., 2017; Seitz et al., 2016) in individuals with chronic schizophrenia-spectrum disorders.

In FEP individuals, white matter microstructure abnormalities were also observed at a whole-brain level, characterised by decreased FA predominantly in the corpus callosum bilaterally, and extending into the right posterior thalamic radiation, and the posterior corona radiata, and increased RD across a number of regions including the corpus callosum, anterior thalamic radiation, forceps major, UF, superior longitudinal fasciculus, and forceps minor, and the inferior fronto-occipital fasciculus bilaterally. However, neither the ROI nor tractography analyses revealed any microstructure abnormalities in the WM tracts of interest in the current study in FEP individuals compared to younger healthy controls. White matter findings in FEP individuals are incredibly inconsistent, with some studies finding no microstructure or connectivity abnormalities in these individuals (Friedman et al., 2008; Kong et al., 2011; Peters et al., 2008; G. Price et al., 2005; Qiu et al., 2009; White et al., 2011), and others finding mild (M. A. Di Biase et al., 2017; Seitz et al., 2016; Zhou et al., 2017) or even widespread abnormalities (Alvarado-Alanis et al., 2015; Lee et al., 2013; Melicher et al., 2015). Thus, while some studies have identified abnormalities in our ROIs in FEP individuals (Zhou et al., 2017), these findings are not consistent across all FEP studies. Interestingly, previous studies have found that lower FA in the cingulum bundle and fornix is a predictor of poorer prognosis or response to treatment in FEP individuals and individuals with chronic schizophrenia-spectrum disorders (Keymer-Gausset et al., 2018; Mitelman et al., 2006; Reis Marques et al., 2014). Additionally, white matter microstructure abnormalities in the fornix

and ventral cingulum have been associated with increased psychopathology in individuals with schizophrenia-spectrum disorders (Abdul-Rahman et al., 2011). It is thus possible that a lack of findings in our study is suggestive of good clinical prognosis for these FEP individuals – a finding which is consistent with their relatively mild symptom profiles compared to FEP individuals in other studies. It is also worth noting the differential findings in the UF between our whole brain analysis, which revealed increased RD in this tract bilaterally, and our ROI findings, which revealed no difference between FEP individuals and healthy controls in the UF after correcting for multiple comparisons. This discrepancy likely reflects one of the issues with ROI approaches, such that averaging across an entire tract may potentially mask abnormalities that are circumscribed to only part of that tract.

Our findings in both FEP individuals and those with chronic schizophrenia-spectrum disorders suggest that abnormalities in radial, rather than axial diffusivity may represent a key pathological marker in individuals with chronic schizophrenia-spectrum disorders. Radial diffusivity is typically considered to be a measure of myelination (Song et al., 2002), whereas axial diffusivity measures axonal integrity or injury (Song et al., 2003). The current findings therefore suggest that white matter abnormalities in chronic schizophrenia-spectrum disorders may be driven by demyelination rather than a reduction in axonal density. This is consistent with previous studies showing in vivo MRI-derived reductions in myelination, as measured by myelin water fraction, in both early and chronic schizophrenia-spectrum disorders (Flynn et al., 2003; Lang et al., 2014; Vanes et al., 2019, 2018). This is also consistent with post-mortem studies showing reductions in the number of oligodendrocytes and their associated proteins in individuals with schizophrenia-spectrum disorders (Flynn et al., 2003; Takahashi et al., 2011; V. M. Vostrikov et al., 2007; V. Vostrikov & Uranova, 2011).

6.3.2. Memory impairment is related to hippocampal subfield volumes in FEP individuals and individuals with chronic schizophrenia-spectrum disorders

Despite observing hippocampal volume reductions only in individuals with chronic schizophrenia-spectrum disorders, relationships were observed between hippocampal subfield volumes and memory performance in both FEP individuals and those with chronic schizophrenia-spectrum disorders. Interestingly, the same subfields were implicated across both patient groups – namely, volume reductions in the SRLM, and CA4DG were associated with poorer visual associative memory performance across both patient groups. Only one previous study has identified relationships between hippocampal subfield volumes and

memory performance in chronic schizophrenia-spectrum disorders (Mathew et al., 2014), which found left CA1, CA2/CA3, subiculum, and CA4/DG volumes were positively associated with list learning performance, a measure of verbal memory. A second study of individuals with chronic schizophrenia-spectrum disorders failed to detect relationships between measures of verbal memory and hippocampal subfield volumes, despite observing subfield volume reductions in these individuals (Haukvik et al., 2015). However, this study only tested relationships between memory ability and subfield volumes in regions that differed in volume between individuals with schizophrenia and bipolar disorder (i.e. subiculum and presubiculum), therefore it is not possible to determine whether relationships may have existed with other hippocampal subfields in these individuals. Finally, a study of FEP individuals also failed to detect relationships between measures of verbal memory and hippocampal subfield volumes (Briend et al., 2020), although volume reductions were again present in this sample. Given that, as discussed previously, verbal memory ability is also heavily influenced by a number of other cognitive processes, including verbal knowledge (Jordan et al., 2013), it is therefore possible that the PAL task is more sensitive to illness-related abnormalities in the hippocampus, particularly in early illness stages, when deficits may be more subtle.

Distinct hippocampal subfields are thought to play different roles in memory encoding and retrieval. The dentate gyrus is the input region of the hippocampus, and evidence suggests that it acts as a pre-processor of incoming information (Jonas & Lisman, 2015). One of the key functions of the dentate gyrus is pattern separation, an encoding mechanism in which relatively similar input patterns are transformed into highly distinct output patterns (Leutgeb et al., 2007; O'Reilly & McClelland, 1994; Tamminga et al., 2010). Pattern separation is also carried out by the CA3, however, this region, together with the CA1, is also responsible for pattern completion (Tamminga et al., 2010). Pattern completion occurs during memory retrieval, when original patterns of activation that occurred during memory encoding are reinstated from partial stimuli cues (Hunsaker & Kesner, 2013; Mathew et al., 2014). Connectivity between these subfields is facilitated by the hippocampal SRLM. Specifically, the stratum lacunosum-moleculare contains fibers from the perforant path, which connects the entorhinal cortex to CA1 (Maccaferri, 2011), whereas the stratum radiatum is largely involved in connecting the CA3 and CA1 subfields (Witter, 2007a). Our findings therefore suggest that memory impairment in individuals with schizophrenia-spectrum disorders may be related to deficits in dentate gyrus-mediated pattern separation, as well as possible

disruptions to pattern completion processes in the CA3 and CA1, which would rely on effective connectivity through SRLM.

In *Study 2* we hypothesised that relationships between SRLM volumes and memory performance may reflect the impact of illness-related stress on this particular subfield, and it is possible that similar mechanisms underlie the relationship between memory performance and CA2CA3 volumes. The stratum radiatum and stratum lacunosum-moleculare layers of the hippocampus contain the apical and terminal dendrites of CA1 pyramidal cells respectively, as well as some of the axons of the perforant pathway, which connects the entorhinal cortex to the hippocampus (Witter, 2007b). The CA1 is considered to be a critical region involved in the formation, consolidation, and retrieval of hippocampal-dependant memories. Similarly, the CA2CA3 is thought to play a role in pattern separation and pattern completion, and is critically involved in associative memory ability (Nakazawa et al., 2002, 2003; Rajji et al., 2006). Chronic exposure to stress hormones has been shown to cause apical dendritic retraction in the hippocampus (B S McEwen, 2000; Woolley et al., 1990), including in the CA1 stratum radiatum (Chen et al., 2010) and in the CA3 (Christian et al., 2011). Further, stress-induced dendritic retraction has been shown to cause impairments in spatial memory ability (Aguayo et al., 2018; Conrad, 2006; Bruce S. McEwen et al., 2016). Though much of the current evidence to support the notion of stress-induced brain atrophy is derived from animal studies, this hypothesis is consistent with findings of relationships between impaired cognitive functioning and abnormalities in the Hypothalamic-Pituitary-Adrenal (HPA) axis, including increased cortisol levels, in individuals with schizophrenia-spectrum disorders (Aas et al., 2011; Lupien, 2000; Walder et al., 2000). Importantly, this chronic stress-induced dendritic retraction appears to be reliant on NMDA receptors (Christian et al., 2011; Magarinos & McEwen, 1995), with chronic stress causing changes in NMDA receptors and increased glial glutamate transporter 1 (GLT-1) expression within the hippocampus (Lowy et al., 1993; Watanabe et al., 1995; G. E. Wood et al., 2004).

The other subfield that showed a relationship with memory performance across both patient groups was the CA4DG. The granule cell layer of the dentate gyrus is one of the few sites of adult neurogenesis in humans, and adult-born DG neurons are thought to play a crucial role in episodic memory formation (Benarroch, 2013; Drew et al., 2013; Gonçalves et al., 2016), particularly for spatial memories (Snyder et al., 2005). In individuals with schizophrenia-spectrum disorders however, there is postmortem evidence for reduced proliferation of adult-

born dentate gyrus granule cells (Allen, Fung, & Weickert, 2016; Reif et al., 2006), which may contribute to both hippocampal volume reductions and memory impairments in this population, though these studies are limited to individuals with chronic schizophrenia-spectrum disorders. The dentate gyrus also forms part of the perforant path, receiving inputs from the entorhinal cortex and projecting via mossy fibres into CA3 (Amaral et al., 2007). This pathway is critical for associative memory formation (Carr et al., 2017), and it is therefore plausible that disruptions to one of the key subregions within this network would result in deficits in visual associative memory. Functioning of the DG within the perforant pathway relies on glutamate-mediated signalling via NMDA receptors (Lavenex & Amaral, 2000; Staples et al., 2015; Stein et al., 2015; Zola-Morgan & Squire, 1993), which comprise different subunits, including GluN1 and GluN2s. It is also possible that glutamatergic dysfunction within the dentate gyrus may exert downstream effects on the CA3 (Tamminga et al., 2012), which is itself an important region for the encoding of spatial information and the acquisition of relational associations (Kesner, 2007), which are both key aspects of visuospatial associative memory. Specifically, reduced glutamate signalling in the dentate gyrus has been posited to sensitise CA3 pyramidal neurons to incoming stimuli, resulting in higher levels of neuronal activity in CA3 (Tamminga et al., 2012). Given the important role of the CA3 in forming associations, increased sensitivity to incoming stimuli in this region could potentially lead to a rise in false associations (Tamminga et al., 2012). Though speculative, this model could further explain the observed relationship between CA4DG volumes and PAL performance in both FEP individuals and individuals with chronic schizophrenia-spectrum disorders.

6.3.3. Memory impairment is related to abnormal white matter microstructure in individuals with a chronic schizophrenia-spectrum disorder but not a FEP illness

Study 3 aimed to investigate whether impairments in visual associative memory ability were related to abnormal white matter microstructure in FEP individuals and those with chronic schizophrenia-spectrum disorders. Our findings revealed that white matter microstructure was related to memory ability in individuals with chronic schizophrenia-spectrum disorders and younger healthy controls. Specifically, ROI analyses of select white matter tracts revealed that poorer visual associative memory was associated with increased RD and AD in the fornix, and with increased RD in the left dorsal cingulum bundle, in individuals with chronic schizophrenia-spectrum disorders. Additionally, poorer visual associative memory was related to increased hippocampal-thalamic RD and AD in the right hemisphere in

individuals with chronic schizophrenia-spectrum disorders. Poorer PAL performance was also associated with reduced FA and increased RD between the hippocampus and the thalamus in the left hemisphere in younger healthy controls. These findings suggest that abnormal white matter microstructure of the fornix, the cingulum bundle and in the pathway between the hippocampus and the thalamus is implicated in memory impairment in individuals with chronic schizophrenia-spectrum disorders, when white matter abnormalities are evident in the illness relative to healthy controls.

Observed relationships between fornix white matter microstructure abnormalities and poorer memory performance in individuals with chronic schizophrenia-spectrum disorders are consistent with previous studies, which have identified relationships between white matter microstructure in the fornix and performance on tasks of episodic memory, not only in individuals with chronic schizophrenia-spectrum disorders (Green et al., 2016; Nestor et al., 2007; Takei et al., 2008), but also in healthy children and younger and older adults (V. Douet et al., 2014; Metzler-Baddeley et al., 2011; Rudebeck et al., 2009; Zahr et al., 2009), and in Alzheimer's disease (Ji et al., 2019; Nowrangi & Rosenberg, 2015; Zhuang et al., 2013). These findings are also consistent with the critical role of the fornix in connecting the hippocampus to other regions within the hippocampal-prefrontal network, including the anterior cingulate cortex, nucleus accumbens, striatum, medial prefrontal cortex, and septal regions (Bubb et al., 2017; Vanessa Douet & Chang, 2015; Parent et al., 2010). Given that performance on paired associate learning tasks is dependent upon concurrent activation of the hippocampus and the prefrontal cortex (Eichenbaum, 2017; Preston & Eichenbaum, 2013; Simons & Spiers, 2003), which is supported by the fornix, it is certainly plausible that microstructural abnormalities in the fornix could contribute to memory impairment in schizophrenia-spectrum disorders. Our findings are thus consistent with the functional role of the fornix, and with previous white matter studies, yet extend upon them by demonstrating that abnormal AD in the fornix is also associated with memory impairment in individuals with chronic schizophrenia-spectrum disorders but not FEP individuals. It is also the first study to identify these relationships in a test of non-verbal episodic memory and the first to examine relationships between measure of FA, RD, or AD and memory performance in FEP individuals.

In *Study 3* we also found that memory performance was related to white matter microstructure in the hippocampal-thalamic pathway in both individuals with chronic

schizophrenia-spectrum disorders and younger healthy controls. Our findings of relationships between hippocampal-thalamic white matter microstructure and memory performance in individuals with chronic schizophrenia-spectrum illness and younger healthy controls are also consistent with an important role this pathway plays in facilitating connectivity between the hippocampus and the mPFC (Aggleton et al., 2010; Dolleman-ven der Weel et al., 2019; Pergola & Suchan, 2013; Zola-Morgan & Squire, 1993). Connectivity between the hippocampus and the thalamus is considered critical for memory performance (Aggleton et al., 2010; Bubb et al., 2017; Dolleman-ven der Weel et al., 2019), and our findings show that such connectivity extends to measures of white matter microstructure, not only in individuals with schizophrenia-spectrum disorders, but also in healthy young adults. Interestingly, it has previously been proposed that elevated glutamate resulting from NMDA receptor dysfunction in the hippocampus could also lead to excitotoxic effects on anterior thalamic GABAergic interneurons, indicating that the thalamus may also be a key site of NMDA receptor dysfunction in schizophrenia-spectrum disorders (Howes et al., 2016; Stone et al., 2007). Furthermore, dysfunction of GABAergic interneurons in the anterior thalamus could cause activation of glutamatergic thalamocortical projection neurons, which would, in turn, lead to increased cortical glutamate release in the anterior cingulate cortex (Stone et al., 2007). Perhaps most importantly for our white matter findings, excess glutamate has been shown to be toxic to white matter oligodendrocytes and to damage myelin (Dias, 2012; Matute et al., 2007). Previous studies have not examined relationships between hippocampal-thalamic white matter microstructure and memory performance in individuals with schizophrenia-spectrum disorders, and our findings therefore constitute a novel contribution to the literature.

As discussed in *Study 3*, the results that, in individuals with chronic schizophrenia-spectrum disorders, poorer memory performance was associated with increases in both radial *and* axial diffusivity in the fornix and the hippocampal-thalamic pathway was contrary to our hypothesis that memory impairment would be associated with reduced AD. Myelin pathology is thought to be represented by *increases* in RD, however, axonal pathology is typically associated with *decreases* in AD, which measures the rate of diffusion along the principal axis of a fibre bundle (Budde et al., 2009; Song et al., 2003). Based on these conventions, we would expect to see poorer memory performance associated with reduced axial diffusivity. However, findings regarding AD in previous studies are far from consistent, and a number of studies have found increased AD to be associated with poorer behavioural outcomes and

increased neurodegeneration across a range of diseases, in ageing individuals, and in those with traumatic brain injury (Arfanakis et al., 2016; Della Nave et al., 2011; Lancaster et al., 2016; Mayo et al., 2019; Mielke et al., 2012; Newcombe et al., 2011). One potential explanation for these findings is that cellular necrosis or reductions in axonal density in these regions may lead to encroachment of cerebrospinal fluid, resulting in less restricted diffusion both radially and axially. Alternatively, increased axial diffusivity may reflect changes in the dominant cell type contributing to the diffusion signal – for example, increased numbers of microglia or astrocytes replacing axonal bundles, leading to increased diffusion in all directions (Newcombe et al., 2011). Without complementary assays (for example, histology) it is not possible to determine the exact mechanisms underlying increased axial diffusivity in the current study. However, it is clear that they are related to pathological processes that are occurring only in the most chronically ill patients, and not in those experiencing FEP. The FEP period may therefore represent a critical period in which early intervention is essential to prevent these ongoing pathological processes.

Laterality differences between individuals with chronic SSD and younger healthy controls (with the left hemisphere implicated in younger controls and the right hemisphere in chronic schizophrenia-spectrum disorders), in the hippocampal-thalamic pathway could potentially be explained by laterality differences in the encoding and retrieval of episodic memories. The hemispheric encoding/retrieval asymmetry model posits that the left prefrontal cortex is biased for *encoding* of both verbal and non-verbal memories, whereas the right prefrontal cortex is biased for verbal and non-verbal memory *retrieval* (Habib et al., 2003). It is therefore possible that in healthy young adults, superior memory performance is facilitated by an enhanced ability to encode memories, whereas in individuals with chronic SSD, retrieval deficits may be driving poorer memory performance. The finding in younger healthy controls is consistent with the fact that relationships in this group were observed for measures of FA and RD, suggesting that myelination may be key in this group. Myelination has been shown to play an important role in circuit plasticity, and recent studies have demonstrated that activity-dependent formation of myelin in the circuits encoding memory contributes to memory consolidation and recall (Fields, 2015; Fields & Bukalo, 2020; Pan et al., 2020; Steadman et al., 2020). Thus, the relationships observed in younger healthy controls likely reflects normal neurodevelopmental processes, which have potentially started to break down in some older healthy controls. This is consistent with previous studies, which have shown that encoding processes deteriorate as healthy individuals age (Cadar et al., 2018; Morcom et

al., 2003), and with the fact that, in the current study, age as a covariate substantially impacted on the relationship between hippocampal-thalamic FA and PAL performance.

Finally, it is important to note that, although we set out to map connectivity between the hippocampus and the medial prefrontal cortex directly, the results of tractography between these regions produced potentially unreliable data, and these analyses were therefore disregarded. Specifically, across both hemispheres, a number of participants had either no tracts generated or a very low number of tracts generated (<10). Direct connections between the hippocampus and the prefrontal cortex are relatively sparse (Godsil et al., 2013), and it is possible that our data reflects this, particularly in individuals with chronic schizophrenia who have demonstrated white matter disruptions. Visual inspection of the data also revealed that two different pathways were being tracked across participants, with some individuals showing pathways in the cingulum bundle, some in the inferior fronto-occipital fasciculus, and others a combination of the two. Evidence from rat studies suggests that there are two direct pathways from the hippocampus to the prefrontal cortex: a pathway from the ventral CA1 and subiculum that enervates the medial prefrontal cortex, and a pathway from the dorsal hippocampus to the anterior cingulate cortex (M. Li et al., 2015). It is therefore possible that our medial prefrontal cortex mask may have also captured the anterior cingulate cortex in some participants. However, further eroding these masks would likely have exacerbated the issue of low streamline counts across a larger number of participants. Given the paucity of human imaging studies examining hippocampal-medial prefrontal white matter connectivity, it is clear that this is an important avenue for future studies.

6.4. Memory impairment in the absence of brain abnormalities in FEP individuals

Given that memory impairment was observed in the FEP sample used in *Chapters 4 and 5*, it was surprising that no volume reductions were observed across any hippocampal subfield, and no white matter microstructure abnormalities were observed in any hippocampal-prefrontal region of interest or tractography-generated tract. These findings are consistent with other studies that have utilised the same FEP cohort, and failed to detect any abnormalities in resting-state functional connectivity or topology in these individuals (Ganella et al., 2018). This raises the question whether memory impairments appear prior to observable brain abnormalities in key memory-related regions in FEP individuals. This is certainly possible, although longitudinal studies would be required to determine whether this

is the case. It is also possible that, given our small sample size, we simply did not have enough power to detect brain abnormalities, which are often quite subtle in FEP individuals, in the regions of interest in our current sample. It is also possible that the finding of memory impairments in this group were driven by a small sub-group of poorly performing patients, which can be seen in Figure 2 in *Study 2*. It is therefore possible that brain abnormalities in the poorly performing sub-group are being masked by a lack of volume reductions in the subgroup whose performance is in line with younger healthy controls. This is consistent with our observed relationships between PAL performance and subfield volumes in the FEP cohort – that is, hippocampal abnormalities are greater in those with worse memory performance.

These findings are also consistent with the notion that brain abnormalities are heterogeneous in schizophrenia-spectrum disorders, particularly for those in the early stages of the illness. The reasons for this heterogeneity are many and varied, with factors such as illness duration, medication dosage and type, and symptom severity all associated with hippocampal volumes in schizophrenia-spectrum disorders (Bodnar et al., 2016; Chakos et al., 2005; Mamah et al., 2012; Velakoulis et al., 1999, 2006). Given that these factors vary widely between studies, it is not surprising that hippocampal subfield volume abnormalities are present (or absent) to a different degree across FEP studies. Furthermore, a number of studies have made use of segmentation pipelines that have since been shown to produce unreliable volume estimates that are inconsistent with brain anatomy – particularly Freesurfer version 5.3 (de Flores et al., 2015; Pluta et al., 2012; Whelan et al., 2016; Wisse et al., 2014). These issues are more likely to affect samples in which abnormalities, if they are present, are more subtle – which would appear to be the case for FEP individuals (Gary Price et al., 2010).

It is also worth noting that, while no white matter abnormalities were present in our white matter ROIs or tractography-generated tracts, whole-brain voxel-wise analysis of white matter microstructure did reveal reduced FA and increased RD in the current FEP sample. Although no relationships between these abnormalities and memory performance were observed on a whole-brain level, it is possible that any potential relationships between these measures may be masked by the need to correct for multiple comparisons over the entire brain, especially given the small sample size of the FEP cohort. It is also possible that FEP individuals still have a degree of brain plasticity at this early illness stage, and therefore

compensatory connections may be used for maintaining memory performance in these individuals.

Additionally, given that relationships were observed between memory performance and hippocampal subfield volumes but not white matter indices in our FEP sample, it is possible that, in FEP individuals, memory impairment is driven primarily by abnormalities *within* key brain structures, such as the hippocampus, rather than by disrupted connectivity between brain regions. Previous studies have demonstrated that grey matter pathology in SSDs is related to connectivity disruptions (Maria Angelique Di Biase et al., 2019; Wannan et al., 2019), and evidence from grey- and white-matter studies suggests that cortical grey matter pathology precedes white matter deficits in schizophrenia-spectrum disorders (Cropley et al., 2017; Maria Angelique Di Biase et al., 2019; Hulshoff Pol et al., 2002; Kochunov et al., 2013; Nenadić et al., 2012; Zhang et al., 2015). It is therefore possible that abnormalities within the hippocampus might drive microstructural abnormalities in white matter tracts that are connected to this structure, with the degree of white matter impairment increasing as the illness progresses and the level of hippocampal pathology increases. Thus, relationships with measures of white matter microstructure might be more prominent in later illness stages, as we found in the current study. However, this hypothesis is currently speculative, and further longitudinal studies are required to determine whether hippocampal pathology might drive white matter abnormalities in related tracts, and how this might lead to worsening memory performance.

6.5. Implications for the clinical staging model and neurodevelopmental vs neuroprogressive hypotheses of schizophrenia-spectrum disorders

Taken together, our studies have provided both cognitive and neuroimaging evidence in support of a clinical staging model of schizophrenia-spectrum disorders, whereby individuals in a more chronic illness stage present with more severe deficits than those in the early stages of the illness. In FEP individuals, visual associative memory was either preserved or only mildly impaired relative to healthy individuals, whereas the degree of impairment observed in individuals with chronic illness was substantial. Similarly, hippocampal subfield volume loss and white matter abnormalities in the hippocampal-prefrontal pathway were only observed in individuals with chronic illness, with FEP individuals exhibiting no abnormalities. Thus, it

would appear as though moving to a later more chronic illness stage, characterised by severe symptoms, is associated with more severe cognitive and brain abnormalities.

Furthermore, our finding of longitudinal deterioration of visual associative memory following psychosis onset could suggest that the more severe cognitive and brain abnormalities observed in individuals with chronic illness could reflect neuroprogressive processes that occur with ongoing illness. This notion is supported by previous studies, which have provided evidence for progressive volume loss across hippocampal subfields in FEP individuals and those with recent-onset schizophrenia-spectrum disorders (N. F. Ho et al., 2016; Kawano et al., 2015; W. Li et al., 2018; Rhindress et al., 2017), and with studies demonstrating progressive white matter abnormalities in individuals with FEP and chronic schizophrenia-spectrum disorders .

However, another possible explanation for our findings in FEP individuals versus those with chronic illness is that the more severe brain abnormalities observed in individuals with chronic illness are a result of sampling bias. That is, studies of individuals with chronic illness may be biased toward recruitment of individuals at the more severe end of the illness spectrum – such as those who are hospitalised or still engaged with mental health services (Guloksuz & van Os, 2018). This is potentially reflected in the more severe positive and negative symptoms and the greater degree of functional impairment observed in our chronic illness sample relative to our FEP sample. It is therefore possible that our neuroimaging results in FEP individuals and those with chronic illness do not reflect progressive deterioration but might rather suggest that there are distinct subgroups of patients with varying degrees of cognitive and functional impairment and brain abnormalities. Thus, patients with more severe illness may present with more severe brain abnormalities, regardless of their illness stage, with a stable trajectory present from the time of illness onset. Our chronic sample may therefore have been biased towards a particular subgroup of patients with more severe symptoms, functional and cognitive impairment, and brain abnormalities. However, given that numerous longitudinal studies have identified progressive brain abnormalities in individuals with psychotic illnesses, particularly in the early stages of these disorders (Cali F Bartholomeusz et al., 2016), it is unlikely that more severe brain abnormalities in individuals with chronic illness are due entirely to sampling bias.

A more likely possibility is that notions of illness subgroups, clinical stages, and neurodevelopmental versus neuroprogressive processes are not mutually exclusive, but rather co-exist within an illness population. For example, it is possible that different combinations or severities of neurodevelopmental insults, such as polygenic risk, prenatal or perinatal insults, or early childhood experiences, may lead to differing illness severities and trajectories – and thus different patient subgroups – in individuals with schizophrenia-spectrum disorders. This is consistent with previous studies, which have identified the distinct cognitive subgroups within samples of individuals with schizophrenia-spectrum disorders, including those with preserved cognitive functioning, those with moderate or severe impairment, and those with a deteriorated cognitive ability (Carruthers et al., 2019; Van Rheenen et al., 2020, 2018; Weinberg et al., 2016; Woodward & Heckers, 2015). Interestingly, these subgroups have been shown to be characterised by different clinical and functional outcomes and brain structure. Though the relatively small sample sizes of our studies make it difficult to investigate different illness subgroups, this appears to be a promising way forward for future studies, particularly those with longitudinal designs. Such studies could attempt to answer questions raised by our current work, including whether progressive cognitive and brain structural abnormalities are present only in particular subgroups of patients. The presence of stable versus deteriorating subgroups may also be integrated into a clinical staging model to inform treatment strategies that are aimed at either preventing deterioration or remediating deficits, as we have proposed previously (Christos Pantelis et al., 2015).

6.6. Limitations and future directions

The studies presented in this thesis had several limitations, which should be noted when considering the wider implications of our findings. The first limitation relates to possible effects that varying schizophrenia-spectrum diagnoses or phenotypes may have on both cognition and neurobiological processes, which were not accounted for or investigated in these three studies. Schizophrenia-spectrum disorders is an umbrella term used to describe several distinct clinical diagnoses, such as schizophrenia, schizoaffective disorder, delusional disorder, and schizophreniform disorder. While a number of studies have found that individuals with schizophrenia may present with more severe brain abnormalities (Birur et al., 2017; Zhang et al., 2020), cognitive impairment (Barch & Sheffield, 2014; Bora et al., 2009; Lynham et al., 2018; Torniainen et al., 2012), and cognitive decline (Zanelli et al.,

2019) than those with other psychoses, such as schizoaffective disorder or affective psychosis, others have found that the various psychoses are difficult to distinguish on a cognitive or neurobiological level (Amann et al., 2016; Bora et al., 2010; Guloksuz & van Os, 2018; Landin-Romero et al., 2016). Further to this, it has been suggested that schizophrenia-spectrum illnesses be considered not as distinct diagnoses, but rather as a continuum of psychosis characterised by illness severity (Guloksuz & van Os, 2018). Our studies are based on a categorical model of schizophrenia-spectrum illness, in which inclusion in a study is determined by the presence of a formal diagnosis of a schizophrenia-spectrum disorders, and we have not considered the implication of variations of illness severity within our patient groups.

A second limitation lies in the small sample of FEP individuals utilised in *Chapters 4 and 5*. As we have discussed above, it is certainly possible that our null findings in terms of brain abnormalities in FEP individuals across two studies reflects the fact that these studies were underpowered. Underpowered studies can produce unreliable findings for a number of reasons, including failure to detect a true effect, and either under- or over-estimation of an effect when a positive effect is identified (Button et al., 2013). It is therefore possible that our small sample size did not provide us with the necessary power to detect differences in hippocampal subfield volumes or white matter microstructure in our FEP sample. However, findings of relationships between memory performance and hippocampal subfield volumes in the same regions in FEP individuals and those with chronic schizophrenia-spectrum disorders provides some indication that these findings are not due to false positives (though we cannot eliminate the possibility that the magnitude of these relationships were either over- or under-estimated). Limitations in sample size also make it difficult to investigate clinical sub-groups, as discussed above, which may provide more meaningful findings than simply categorising individuals as FEP or healthy control. For example, it may be of interest to examine brain abnormalities across FEP individuals with poor versus preserved memory performance, however this was not possible due to the very small number of participants exhibiting substantial impairments on the PAL task relative to younger healthy controls.

Third, it was not possible across any of our studies to examine the effects of cumulative medication exposure on either cognitive performance or brain structure, or on the relationships between these factors. Higher cumulative antipsychotic dose has been associated with poorer cognitive performance and smaller grey matter volumes (B.-C. Ho et

al., 2011; Husa et al., 2017), and it is therefore possible that cumulative exposure to antipsychotic medication could have influenced our findings. While we did examine relationships between current antipsychotic medication dosage and our variables of interest, and found no relationships, measures of cumulative exposure were not collected and therefore these relationships could not be examined. Thus, it is unclear the extent to which our findings may be related to the effects of antipsychotic medication on the brain or on cognitive functioning.

Finally, it was unfortunate that there were no data relating to verbal episodic memory ability in our cross-sectional studies, particularly as verbal associative memory has similarly been found to be preserved in FEP individuals (C F Bartholomeusz et al., 2011). Additionally, the verbal memory task used in *Study 1* was not overly comparable to the CANTAB PAL task in terms of task complexity or ability to measure associative memory. An appropriate verbal memory task would have provided an interesting comparison against which to contrast (or confirm) our visual memory findings – particularly given recent high-quality longitudinal findings suggesting that verbal memory does, in fact, deteriorate following psychosis onset (Zanelli et al., 2019). A focus for future studies will therefore be to examine verbal episodic memory performance longitudinally following psychosis onset, and to examine the neural correlates of this area of functioning across multiple time-points and illness stages.

In order to overcome the above limitations, we suggest that future studies focus on developing large samples of clinically heterogeneous patients, whose illness severity lies across the psychosis continuum. In particular, longitudinal studies that track illness progression from the psychosis prodrome or first full-threshold psychotic episode would help to further disentangle how early illness factors, including cognitive ability and brain structure and function, might be related to later disease chronicity or remission, or with varying clinical phenotypes or treatment response. Such studies may also help to determine how antipsychotic medications affect the brain and its functions over the course of schizophrenia-spectrum illness.

6.7. General Conclusions

Through a combination of clinical and imaging work across illness stages, this thesis has contributed significantly to our understanding of the aetiology and pathophysiology of

schizophrenia-spectrum disorders. Our work demonstrated that, in individuals with FEP, visual associative memory – a measure of episodic memory – was preserved or only minimally impaired. Conversely, in individuals with chronic schizophrenia-spectrum disorders, we observed substantial deficits in visual associative memory. Consistent with these cross-sectional findings, in a long-term follow-up study of FEP individuals, we found that visual associative memory performance deteriorated following psychosis onset. These findings are contrary to the dominant notion of cognitive impairment in schizophrenia-spectrum illness, which posits that cognitive deficits are present at the time of illness onset and remain stable over the course of the illness, and suggest that early intervention may be key in terms of preventing deterioration areas of functioning that are preserved or minimally affected at the time of illness onset (Christos Pantelis et al., 2015). We also found that FEP individuals did not demonstrate reduced hippocampal subfield volumes or abnormal white matter microstructure in key tracts involved in the hippocampal-prefrontal pathway. However, in individuals with chronic schizophrenia-spectrum disorders, volume reductions were observed across a number of hippocampal subfields, and white matter microstructural abnormalities were observed across most of the examined white matter tracts. Relationships between hippocampal subfield volumes were observed across overlapping regions in FEP individuals and individuals with chronic schizophrenia-spectrum illness. However, relationships between white matter integrity and memory performance were only seen in individuals with a chronic schizophrenia-spectrum disorder. Our findings point to a number of potential underlying mechanisms, including glutamatergic dysfunction, stress, and inflammation, in the pathophysiology of memory impairment in schizophrenia-spectrum disorders, which will stimulate future research in this area across stages of schizophrenia-spectrum illness.

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APPENDICES

APPENDIX 1:

Progressive Decline in Attentional Set-Shifting Ability In First Episode Schizophrenia: A 7-year Follow-up Study

Progressive Decline in Attentional Set-Shifting Ability in First Episode Schizophrenia: A 7-year Follow-up Study

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METHOD

Participants

Patients with first-episode psychosis

First episode psychosis (FEP; $n=75$) patients were recruited from consecutive admissions to Orygen Youth Health – Early Psychosis Prevention and Intervention Centre (EPPIC), Australia between 1993-2001. Details are provided in *Chapter 3*.

Healthy control subjects

Control subjects (CTL; $n=67$) were recruited from the same catchment area.

CANTAB

Instructions for the Spatial Working Memory (SWM) and intradimensional-extradimensional (IDED) Attentional Set-shifting tasks are published elsewhere (Pantelis et al., 2009). The SWM is a self-ordered task requiring participants to ‘search’ through a number of boxes on computer screen in order to locate hidden tokens. The key instruction was that once a token had been located inside a particular box, it would not appear there again during that particular trial. The measure of interest from this task was the total number of ‘between-search’ errors (b-s errors), which index SWM performance. These errors were committed when a subject returned to search a box in which a token had already been found during a previous searching sequence, and are considered to be indicative of working memory failure. ‘Within-search’ errors (w-s errors) are also calculated, and measure when a participant returned to search a box in which a token had already been found during the same sequence in a trial. These errors are thought to reflect attentional lapses.

For IDIED, each subject was required to learn a series of discriminations with only one of two stimulus dimensions (purple-filled shapes or white lines) being relevant at each of the nine stages of the task. At each stage, visual and auditory feedback informed the subject if their response was (in)correct. Following six consecutive correct responses the task progressed to the next stage. The variables of interest included the cumulative attrition and error rates. To compensate for chance levels, an adjusted error rate was calculated for each stage not attempted due to failure.

Data Analysis

Group differences in IDIED attrition rates were analysed using odds ratios (binary variables).

SWM and IDIED errors were over-dispersed and negative binomial regression models were employed using generalised estimating equations in SPSS (version 21.0) to determine

measures that predicted change in error scores over follow-up (Wood et al., 2003). Predictors and covariates in each model were determined *a priori* based on differences between the groups and previous literature showing that age, intellectual ability and SWM (for IDED) (Pantelis et al., 2009) significantly contribute to performance (predictors: group membership; covariates: age, premorbid IQ, SWM b-s errors). Main effects were set at $p < 0.05$ with Bonferroni correction applied to individual coefficients.

The windsorization method was used to deal with outliers by replacing extreme values with a less extreme value (i.e. either the next highest or lowest value). Due to the large number of individual tests conducted, the alpha level was set to $p < 0.01$ for all main effects, and a Bonferroni correction was applied to all between-group analyses with the alpha level set to $p < 0.05$. To maintain transparency, all p values less than 0.05 are presented.

RESULTS

SWM Task Errors. A significant main effect of group was observed for b-s errors (Wald $\chi^2(1)=5.40, p=0.02$) and a main effect of IQ was observed for both b-s (Wald $\chi^2(1)=5.59, p < 0.02$) and w-s errors (Wald $\chi^2(1)=5.76, p=0.02$). There was also a significant group.time interaction for the w-s errors (Wald $\chi^2(1)=6.35, p=0.01$). In contrast, there was no significant group.time interaction for the b-s errors (Wald $\chi^2(1)=0.01, p=0.92$).

IDED Task Attrition (Figure 1a & 1b). There were no significant differences in task attrition between participant groups at each stage of the IDED at baseline (all p values > 0.10). However, there was a significant difference between FEP patients and CTLs at follow-up at the EDS ($\chi^2(1)=4.66, p=0.03$) and EDR ($\chi^2(1)=6.31, p=0.01$) stages.

IDED Task Errors (Figure 2a & 2b).

Early stages: No significant main effects were observed on the first two stages. SWM was the only significant predictor at the C_D (Wald $\chi^2(1)=5.16, p=0.02$), and CD (Wald $\chi^2(1)=17.25, p < 0.01$) and CDR (Wald $\chi^2(1)=13.15, p < 0.01$) stages.

ID stages: At the IDS stage, there was a main effect of SWM (Wald $\chi^2(1)=21.02, p < 0.01$). At the IDR stage, there was a significant main effect of group (Wald $\chi^2(1)=10.57, p=0.01$), SWM (Wald $\chi^2(1)=6.66, p=0.01$), and a group.time interaction (Wald $\chi^2(1)=5.72, p=0.17$).

ED stages: At the EDS stage, there was a significant main effect of group (Wald $\chi^2(1)=8.92, p < 0.01$), IQ (Wald $\chi^2(1)=4.94, p=0.03$), and a group.time interaction (Wald $\chi^2(1)=3.95, p < 0.05$). At the EDR stage, there was a significant main effect of group (Wald $\chi^2(1)=26.53, p < 0.01$), IQ (Wald $\chi^2(1)=4.92, p=0.03$), and SWM (Wald $\chi^2(1)=9.55, p < 0.01$).

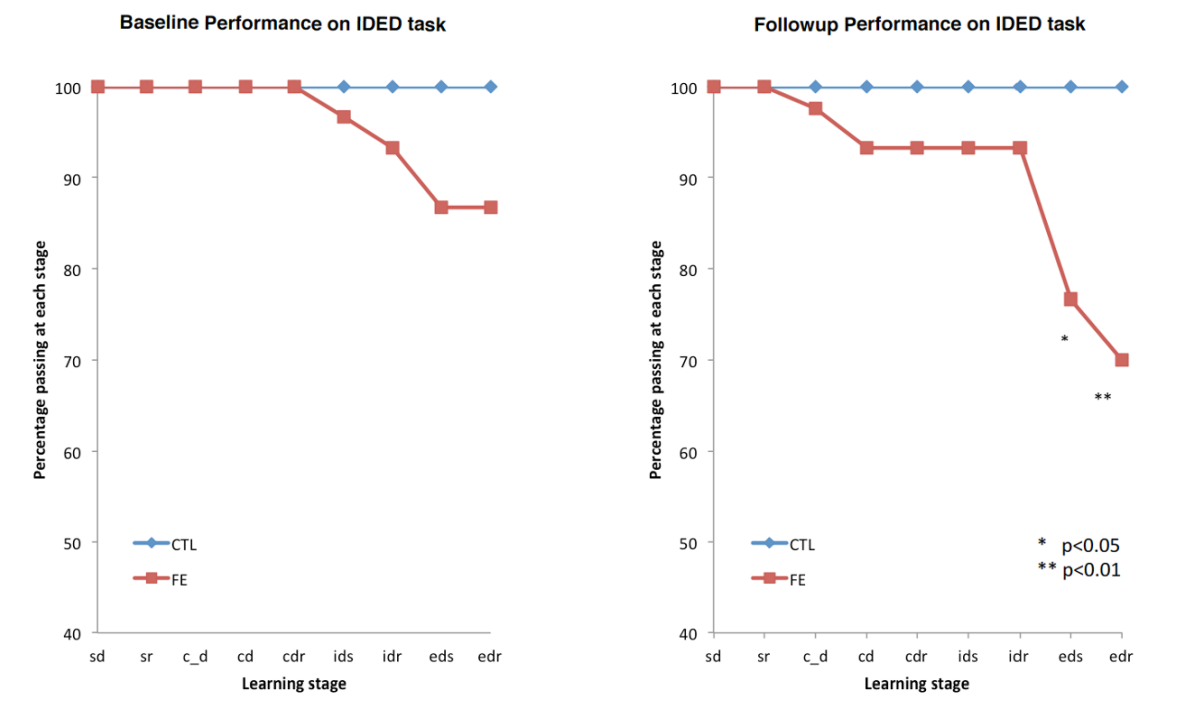


Figure 1a - Cumulative attrition rate on the IED task in healthy control and first episode patients at baseline

Figure 1b - Cumulative attrition rate on the IED task in healthy control and first episode patients at followup

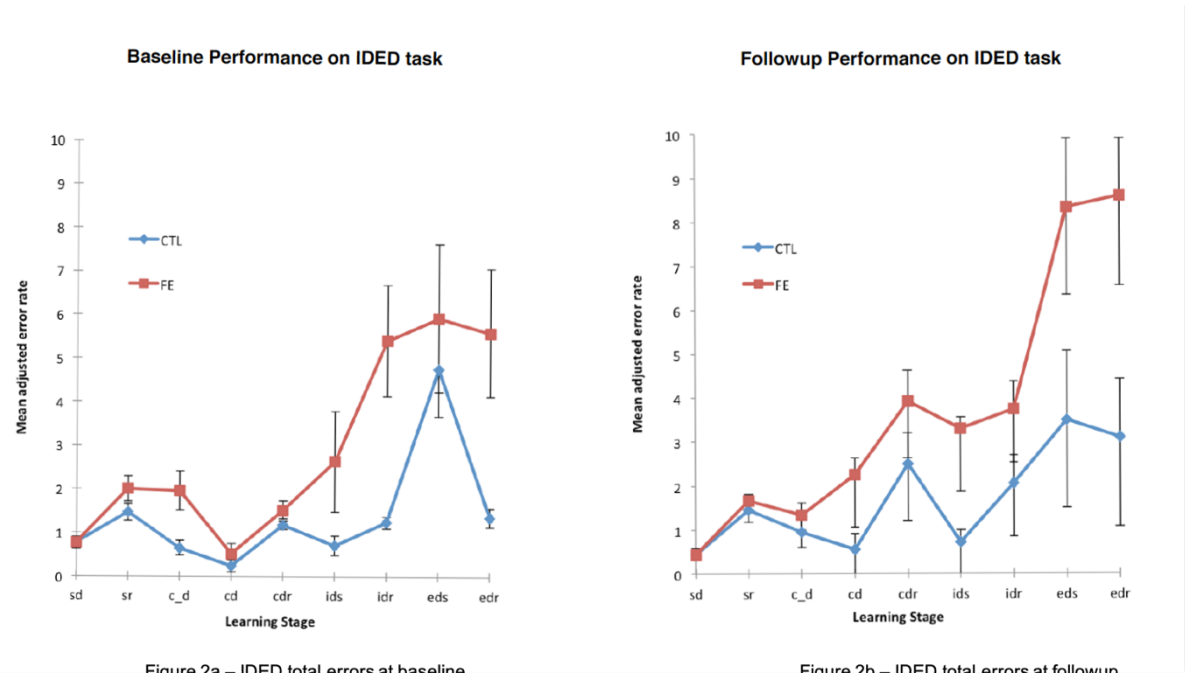


Figure 2a – IDED total errors at baseline

Figure 2b – IDED total errors at followup

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