An investigation of neuroanatomical contributions to cognitive deficits associated with psychotic illness: A 4 year longitudinal follow-up study.

Kenney, Joanne

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An investigation of neuroanatomical contributions to cognitive deficits associated with psychotic illness: A 4 year longitudinal follow-up study.

By

Joanne Kenney BEng, HDip, MSc

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE OF CONTENTS</td>
<td>i</td>
</tr>
<tr>
<td>AUTHORS DECLARATION</td>
<td>iii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>OVERVIEW OF THESIS</td>
<td>vi</td>
</tr>
<tr>
<td>THESIS ABSTRACT</td>
<td>viii</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>x</td>
</tr>
<tr>
<td>FIGURES AND TABLES</td>
<td>xiii</td>
</tr>
<tr>
<td>THESIS INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>COGNITIVE THEORIES OF SCHIZOPHRENIA</td>
<td>1</td>
</tr>
<tr>
<td>DIAGNOSIS &amp; TREATMENT OF COGNITIVE DEFICITS</td>
<td>2</td>
</tr>
<tr>
<td>COGNITIVE DEFICITS IN SCHIZOPHRENIA AND LONGITUDINAL COURSE</td>
<td>3</td>
</tr>
<tr>
<td>LIMITATIONS IN THE LITERATURE ON COGNITIVE COURSE IN SCHIZOPHRENIA</td>
<td>4</td>
</tr>
<tr>
<td>MATRICS CONSENSUS COGNITIVE BATTERY</td>
<td>6</td>
</tr>
<tr>
<td>STRUCTURAL AND DIFFUSION MAGNETIC RESONANCE IMAGING</td>
<td>7</td>
</tr>
<tr>
<td>NEUROANATOMICAL CONTRIBUTIONS TO COGNITIVE DEFICITS</td>
<td>8</td>
</tr>
<tr>
<td>NOVEL ASPECTS OF THE THESIS</td>
<td>10</td>
</tr>
<tr>
<td>OVERALL THESIS AIMS</td>
<td>11</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>13</td>
</tr>
<tr>
<td>PAPER 1</td>
<td>19</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>20</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>21</td>
</tr>
<tr>
<td>METHODS AND MATERIALS</td>
<td>25</td>
</tr>
<tr>
<td>RESULTS</td>
<td>30</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>35</td>
</tr>
<tr>
<td>CONCLUSION</td>
<td>37</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>38</td>
</tr>
<tr>
<td>PAPER 2</td>
<td>43</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>44</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>45</td>
</tr>
<tr>
<td>METHODS AND MATERIALS</td>
<td>51</td>
</tr>
</tbody>
</table>
AUTHORS DECLARATION

I declare that all of the work presented in this thesis was carried out in accordance with the rules and regulations of the National University of Ireland, Galway. This is work is original, except where indicated by reference in the text. This thesis has not been submitted previously for any other academic award.

Original data collected at the time of first psychotic episode was acquired prior to commencement of the current PhD research. Acquisition of MRI and clinical data was acquired by Dr. Cathy Scanlon and Dr. Shane McInerney. Cognitive assessment was acquired Dr. Heike Schmidt at this time. I was responsible for re-recruitment of individuals at follow-up, on average 4 years later, working with Dr. Scanlon and Sophia Arndt, a research assistant. My responsibilities included conducting neuropsychological assessment on a substantial proportion of the sample and re-acquisition of MRI scans at the Centre for Advanced Medical Imaging, St. James’ Hospital as part of the follow-up sample, although these images were not included in the current research. All preprocessing of data and data analysis was conducted by myself, this included scoring neuropsychological tests, preprocessing and quality control of MRI data, tract definition of the arcuate fasciculus and corpus callosum with the assistance of undergraduate students Genevieve McIhlemey and Patrick Corcoran, and working closely with an engineer, Liam Kilmartin, the creation of a new network analysis matlab script for investigating interhemispheric integration. All statistical analysis and writing in the entire thesis was conducted by myself.

Signed: Joanne Kenney
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OVERVIEW OF THESIS

Altered cognition is a core feature of psychotic disorders such as schizophrenia. Kraepelin named the disorder later to be known as schizophrenia, dementia praecox in 1893 (Kraepelin, 1893), which he considered a form of dementia with cognitive deterioration being central to the disorder. Decline in cognition is a valid risk factor for the development of psychosis as it precedes symptomatic manifestation of the illness, which may result from a lag in brain development during adolescence (Thompson et al., 2001). The impact of cognitive deficits in schizophrenia has recently been emphasised by Kahn et al., (2013) who proposed that schizophrenia is primarily a cognitive illness. Certain aspects of cognitive impairment in early stages of psychosis may be prognostic of quality of life (Tolman et al., 2012) and long-term functional outcome (Allott et al., 2011). The central focus of this research is placed on cognitive deficits in the initial stages of psychotic illness and their longitudinal expression involving the examination of cognitive profiles assessed at the time of a first-episode of psychosis and four years later. As the search for reliant imaging biomarkers continues in the early diagnosis of psychosis (Kempton et al., 2015), this research also investigated neuroanatomical factors that may be associated with the most severely impacted cognitive deficits following a psychotic episode.

This thesis is part of a broader longitudinal First Episode Psychosis study which aimed to investigate changes in brain structure and cognition that are associated with psychotic illness. Thirty-six individuals who experienced a first episode of psychosis (FEP) and 59 healthy controls (HC) participated in the initial cognitive and clinical assessments, while 46 individuals with psychosis and 46 controls underwent structural MRI scanning at this baseline time point. On average, four years later at follow-up, participants were re-recruited. Twenty-three individuals with psychosis and 21 controls underwent a cognitive assessment at this second time point, while 28 participants in each group underwent a second structural and diffusion MRI scan. Longitudinal assessment of cognition included data from both baseline and follow-up time-points, while subsequent examinations of the neuroanatomical contributions to cognitive deficits included cross-sectional data from the second follow-up time point, as the diffusion tensor imaging acquisition was included at this time-point only.

This research aims to further extend the etiological understandings of cognitive impairments in psychosis and enable identification of potential neuroanatomical predictors of cognitive deficits early in the disorder. The thesis is distinct in its targeted analysis of specific underlying
neuroanatomical substrates individually customised for each cognitive domain investigated using modern, cutting-edge structural and diffusion magnetic resonance image (MRI) analyses. Three manuscripts have emerged from the current research and are presented in this thesis, the first accepted in *Schizophrenia Research* is titled “Cognitive course in first-episode psychosis and clinical correlates: A four year longitudinal study using the MATRICS Consensus Cognitive Battery”. The second, titled, “The role of the arcuate fasciculus and associated cortices in verbal deficits in psychosis” has been submitted to *Schizophrenia Bulletin* (Nov 2016). And finally, the third manuscript titled “Global brain estimations and speed of processing deficits in psychosis” is in preparation for submission to *Schizophrenia Bulletin*. 
THESIS ABSTRACT

Introduction: In general, individuals who experience a first-episode of psychosis (FEP) display deficits on a wide range of neuropsychological tasks compared to psychiatrically healthy individuals (Bora et al., 2014). Performance is poorer on tasks such as visual learning, working memory, executive functioning, attention, social cognition and processing speed with verbal learning, in particular, being one of the most consistently reported cognitive deficits in schizophrenia (Mesholam-Gately et al., 2009; Aas et al, 2014). This study aimed to examine the trajectory of cognitive deficits after an initial psychotic episode and to identify neuroanatomical abnormalities that are associated with cognitive domains which exhibit the poorest course over time.

Method: Using a cognitive battery specifically designed for researching cognitive impairments in schizophrenia, the MATRICS Consensus Cognitive Battery, this research investigated cognitive deficits at the presentation of a first psychotic episode and four years later. Cognitive profiles of age and gender matched healthy controls were also assessed at the same time points. All participants underwent structural MR scanning at the two time points. Cross-sectional neuroanatomical investigations were conducted with data from the four year time point, which also included a diffusion tensor imaging acquisition. These structural and diffusion MR analyses were conducted to assess whether the presence of neuroanatomical abnormalities was associated with the cognitive domains found to have the most progressive course following a first psychotic episode, namely verbal learning and processing speed. Specifically, (i) the arcuate fasciculus language-related network was investigated in relation to verbal cognition and (ii), due to the global operational nature of processing speed, a specifically chosen selection of global brain estimations were investigated in relation to processing speed deficits.

Results: Individuals with psychosis performed significantly more poorly on all cognitive domains compared to psychiatrically healthy controls. Longitudinally, an initial psychotic episode appeared to be associated with an additional cost on verbal learning and two measures of processing speed over four years as these cognitive domains had marked poorer trajectory compared to the remaining cognitive domains (visual learning, working memory, attention and vigilance, reasoning and problem solving and social cognition). The neuroanatomical substrates for normal processing of verbal cognitive skills appeared to be altered in individuals with recent-onset psychosis, involving an aberrant role of right
hemisphere fronto-temporal cortical regions. In relation to the processing speed composite score, divergent associations of global brain topology and interhemispheric integrity were found in controls and individuals with psychosis particularly with a visuo-spatial subscale, the symbol coding task, which may be indicative of pathology in the global interconnectedness of the brain in relation to processing speed impairments in psychosis. Abnormal associations in temporal lobe efficiency and anisotropy of the genu of the corpus callosum were associated with another visuo-spatial subscale of the processing speed composite score, the Trail Making Test.

**Conclusion:** The findings of this thesis indicate that predominantly deficits of cognition remain stable four years following psychosis onset, with the exception of verbal learning and two measures of processing speed which presented with poorer longitudinal deficits in individuals with psychosis compared with controls. Investigations of the neural substrates of these cognitive domains revealed specific associations between neuroanatomy and cognition which contrasted between individuals with psychosis and controls and may be indicative of abnormalities in the neural substrates underlying verbal learning and processing speed performance in psychosis. In integrating the results of the neuroanatomical investigations, which employ different cognitive and neuroimaging methodologies, evidence emerged for a tentative shared abnormal neural substrate underpinning frontal and temporal regions. The neurodevelopmental model of schizophrenia identifies abnormal development in parietal regions in early adolescence followed by frontal and temporal cortices in later adolescence which coincide with the extent of first-episode psychosis and chronic cases in adulthood. As the course of verbal learning and processing speed follow a less stable trajectory four years following a first-episode, a continuation of these frontal-temporal disturbances may extend throughout illness course resulting in more chronic deficits in these two areas of cognition. Identifying specific anomalies in the brain which are associated with cognitive deficit progression in psychosis carries the potential to be targeted as biomarkers of the disorder, which could be especially beneficial in early disease detection as cognitive impairments primarily predate clinical symptoms.
ABBREVIATIONS

AAL Automated Anatomical Labelling

AF Arcuate Fasciculus

ANOVA Analysis of Variance

AVH Auditory Verbal Hallucinations

BACS-SC Brief Assessment of Cognition in Schizophrenia – Symbol Coding

CPL Characteristic PathLength

CPZ Cholorpromazine

CSA Cortical Surface Area

CSD Constrained Spherical Deconvolution

CSF Cerebrospinal Fluid

CT Cortical Thickness

CV Cortical Volume

DEC-FA Directionally Encoded Colour

DSM Diagnostic and Statistical Manual of Mental Disorders

DTI Diffusion Tensor Imaging

FA Fractional Anisotropy

FDR False Discovery Rate

FEP First Episode of Psychosis

FMRI Functional Magnetic Resonance Imaging

FU Follow-up

GM Grey Matter
HARDI High Angular Resolution Diffusion Imaging

HC Healthy Controls

HMOA Hindrance Modulated Orientation Anisotropy

ICBM International Consortium for Brain Mapping

ICV Intracranial Volume

ITG Inferior Temporal Gyrus

LI Laterisation Index

MATRICS Measurement and Treatment Research to Improve Cognition in schizophrenia

MCCB MATRICS Consensus Cognitive Battery

MPRAGE Magnetization-Prepared Rapid Acquisition of Gradient Echo

MRI Magnetic Resonance Imaging

NART National Adult Reading Test

NIMH The National Institute of Mental Health

PANSS Positive and Negative Syndrome Scale

PCA Principal Component Analysis

PET Positron Emission Tomography

PT Planum Temporale

QLS Quality of Life

RAVLT Rey Auditory Verbal Learning Test

RDOC Research Domain Criteria

SCID Structured Clinical Interview for DSM-IV

SOP Speed of Processing
STG Superior Temporal Gyrus

TMT Trail Making Test

UHG University Hospital Galway

UHR Ultra-High Risk

VF Verbal Fluency

VL Verbal Learning

WM White Matter
FIGURES AND TABLES

Paper 1 Figures:
Figure 1. Four years after illness onset, the first episode psychosis (FEP) group demonstrate significantly lower change in two measures of speed of processing (Trail Making Test; TMT and Verbal fluency; VF) and verbal learning (VL) scores compared to a healthy control (HC) group
Figure 2. Capacity for social cognition and reasoning and problem solving at onset of illness to predict the severity of negative symptoms four years later

Paper 2 Figures:
Figure 1. (A) The three segments of the AF and (B) the combined three segments of the arcuate fasciculus. (C) Seven cortical regions where the arcuate fasciculus is known to project to
Figure 2. The long tract of the arcuate fasciculus was resampled at 32 points along the tract and the fibre bundle reduced to a single averaged tract. ANCOVAs were conducted at each of the 32 points of the reduced average tract, to determine group differences at each point.
Figure 3. (A) Individuals with psychosis performed significantly poorer on verbal learning and verbal fluency compared to healthy controls (HC); (B) Individuals with psychosis had lower cortical thickness compared to healthy controls (HC) in the right hemisphere pars orbitalis which is part of the inferior frontal gyrus
Figure 4. Sections along each of the three segments of the AF that had significant group differences (uncorrected p values)
Figure 5. Figure 5: Reduced surface area (A) and volume (B) in the right STG was correlated with better performance on a verbal fluency task (log transformed) in healthy controls. For the individuals with psychosis, better verbal fluency performance was related to greater volume in the right pars orbitalis (C) while greater volume in the right pars opercularis (D) and reduced left lateralization (volume) of the pars opercularis (E) was associated with better verbal learning performance
Figure 6. Laterality patterns of the long, anterior and posterior segments of the arcuate fasciculus in healthy controls (HC) and individuals with psychosis

Paper 3 Figures:
Figure 1. Mid-sagittal and two para-sagittal AND gates were placed on the DEC-FA map to isolate the corpus callosum
Figure 2. AND gates placed on the DEC-FA maps to isolate the genu (A), body (B) and splenium (C) of the corpus callosum

Figure 3. Bar chart of the group differences on cognitive measures

Figure 4. Using number of streamline weighting, the controls had speed of processing (SOP) composite score was significantly related to global characteristic pathlength (CPL) (A), driven by the relationship with symbol coding (BAC-SC) (B). There also existed a significant association between symbol coding and global efficiency in controls (C) and the trail making test and Global CPL in the psychosis group (D). *Significant correlations. Corresponding non-significant associations found in psychosis and controls are shown in the right panel.

Figure 5. For the individuals with psychosis, higher local efficiency in the right Inferior temporal gyrus and left parahippocampal gyrus was associated with better performance on a visuospatial measure of processing speed (Trail Making Test – Part A).

Figure 6. FA in the genu of the corpus callosum was positively associated with scores on the trail making test (TMT) in individuals with psychosis

Figure 7. Using FA weighting, lower interhemispheric efficiency and higher characteristic pathlength (CPL) were significantly associated with symbol coding in the control group. Using streamline weighting, lower Interhemispheric efficiency was significantly related to symbol coding in controls. *Significant correlations. Corresponding non-significant associations found in psychosis and controls are shown in the right panel

**Paper 1 Tables:**

Table 1. Recent longitudinal studies examining cognitive change across the course of psychosis from the first episode (shaded rows indicate studies with repeated testing of healthy control group included)

Table 2. Demographic Characteristics of the study sample

Table 3. The seven cognitive domains which constitute the MCCB and a description of their respective tests

Table 4. Clinical features at illness onset and follow-up of study sample who were successfully recruited after 4 years (n =23)

Table 5. Baseline and follow-up (FU) cognitive scores of FEP group and healthy controls on the seven cognitive domains of the MCCB

Table 6. Change in scores over time on the cognitive domains and separable cognitive tests of the MCCB

Table 7. Post-hoc analysis of group differences with and without co-varying for speed of processing and verbal learning
Table 1. Demographic characteristics and clinical features of the study sample

Table 2: Correlations between speed of processing composite score (SOP) and individual subscales Trail Making Test, part A (TMT), Brief Assessment of Cognition in Schizophrenia-Symbol Coding (SC), and category fluency test, animal naming (VF) (see Kenney et al., (2015) for description of cognitive tests). All subjects (individuals with psychosis and healthy controls) included (n= 53).

Table 3. Individuals with psychosis had significantly poorer performance compared to healthy controls on all measures of processing speed.
THESIS INTRODUCTION

COGNITIVE THEORIES OF SCHIZOPHRENIA

Schizophrenia is a life-long debilitating mental disorder, characterised by positive and negative symptoms. Positive symptoms include the presence of hallucinations, delusions or thought disorder. Negative symptoms include blunting of affect, poverty of speech and thought, apathy and lack of motivation. While schizophrenia is predominantly defined by these psychotic symptoms, impairments of cognition are also defining and disabling features of the disorder. Kraepelin first defined the disorder as dementia praecox in 1893, what we now know as schizophrenia, which he considered a form of dementia. While the aetiology of schizophrenia is complex, with multiple biological and developmental hypotheses in existence, Kraepelin’s model considered cognitive decline to be the main manifestation of the disorder with deterioration beginning usually around adolescence, much earlier than the emergence of psychotic symptoms. Some theories argue that schizophrenia is primarily a cognitive illness, with the appearance of psychotic symptoms secondary to these cognitive impairments (Kahn et al., 2013). The neurodevelopmental model of schizophrenia is supported by findings that cognition and intellectual impairments are present early in life, several years before the onset of psychotic symptoms (Fusar-Poli et al., 2012; Metzler et al., 2015; Bora et al., 2014). Several studies find that a decline in normal cognitive functioning begins nearly a decade before onset of psychosis, usually during adolescence. In a study of 900,000 Swedish adolescents, poorer scholastic achievement was related to an increased risk of developing schizophrenia, where repeating a school year carried the highest risk and children with the lowest grades had a 4-times increased risk for developing the disorder (MacCabe et al., 2010). In a sample of cognitively impaired individuals with schizophrenia, only 23% had completed their final school examinations (Donohoe et al., 2006).

Additionally, notable cognitive impairments are present in individuals who are at ultra-high risk (UHR) for psychosis (Bora et al., 2014, Fusar-Poli et al., 2012; Bora and Murray et al., 2013 and Rodriguez-Sanchez et al., 2013) where poorer performance on aspects of cognition such as verbal and visual memory, working memory, verbal fluency and executive functioning have been shown to be predictive of conversion to psychosis (Fusar-Poli et al., 2012; Kim et al., 2011, Brewer et al., 2006). While impairments of cognition appear to play a crucial role leading up to emergence of psychosis, generally longitudinal studies show that most of these cognitive deficits appear to remain stable and do not deteriorate further in those who...
convert to psychosis (Metzler et al., 2015). Cognitive ability may therefore reflect a neurodevelopment trait present before first episode manifestation. In recent times, a particular focus in the research has been placed on cognitive deficits in schizophrenia based on evidence that cognitive ability is a significant but modest predictor of quality of life and functioning outcome in people with the disorder, perhaps more so than positive symptoms of the disorder (Green et al., 2000; Nuechterlein et al., 2011; Tolman et al., 2012).

**DIAGNOSIS & TREATMENT OF COGNITIVE DEFICITS**

However, despite the important role which cognitive deficits play in the disorder, they are not included as a ‘criterion A’ symptom of schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders (5th Ed.; DSM-5; American Psychiatric Association, 2013), compared to the inclusion of positive and negative symptoms of the disorder. It was believed that cognition would not be useful as a means of diagnosis. The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) psychosis committee included a dimensional assessment of cognition, in order to emphasise the relevance of cognitive deficits in schizophrenia and the importance of their treatment (Tandon et al., 2013). However, some postulate that it would be beneficial to have a greater diagnostic focus on the changes in cognition that occur premorbid to the emergence of psychosis, the current focus on psychotic symptoms in defining and treating the disorder being too narrow (Kahn et al., 2013). As cognitive deficits have been shown to be a risk factor for schizophrenia (Fusar-Poli et al., 2012), focusing diagnostically on impairments of cognition may facilitate the commencement of certain treatments such as cognitive remediation before psychosis emerges. In line with these proposals, a new research framework for identifying novel ways to study mental disorders has emerged from the National Institutes of Mental Health (NIMH) at the National Institutes of Health (NIH) in the USA, called the Research Domain Criteria (RDoC). This framework encompasses a number of cognitive systems, such as attention and working memory, as a primary criteria domain of the RDoC. However, behavioural constructs of RDoC have not been linked with the pathology domain yet and are recommended for research purpose only, not for diagnosing mental disorders.
COGNITIVE DEFICITS IN SCHIZOPHRENIA AND LONGITUDINAL COURSE

In general, patients with schizophrenia display deficits on a wide range of neuropsychological tasks compared to psychiatrically healthy individuals (Mesholam-Gately et al., 2009; Forbes et al., 2009). Performance is poorer on tasks such as visual learning, working memory, executive functioning, attention, social cognition and processing speed with verbal learning in particular being one of the most consistently reported cognitive deficits in schizophrenia (Toulopoulou and Murray et al., 2004; Mesholam-Gately et al., 2009; Aas et al., 2014). Both verbal learning and processing speed cognitive domains have been noted as prominent impairments in first-episode (Mesholam-Gately et al., 2009) and some studies indicate processing speed to be the most potent predictor of schizophrenia (Dickenson et al., 2007). Executive functioning has also been marked as a specially marked impairment (Reichenberg & Harvey, 2007). A possible overlap between working memory deficits and general cognitive deficits has been reported in schizophrenia (Donohoe et al., 2006), in comparison to other domains such as attentional control which may not be linked to global deficits. The overall degree of cognitive impairment can largely vary between individuals with schizophrenia, with a subgroup displaying more severe cognitive deficits similar to Kraepelin’s description (Roy et al., 2003) and another subgroup with cognitive profiles similar to psychiatrically healthy individuals (Palmer et al., 1997, Donohoe et al., 2006). Meta-analyses reveal that 70%-75% of individuals with schizophrenia have reduced cognitive performance compared to the general population, leaving around 25% of schizophrenia cases in the same range of cognitive ability as healthy individuals (Keefe & Harvey, 2012).

As previously discussed, cognitive deficits are usually present before symptoms emerge (Cornblatt et al., 2016; Seidman et al., 2010); in unaffected first degree relatives of patients in an attenuated form (Asarnow et al., 2002); in remitted patients with schizophrenia (Nuechterlein et al., 1992) and are not accounted for by clinical symptoms (Gold et al., 2004; Bilder et al., 2000). In general, the longitudinal course of cognitive deficits following a first episode of psychosis has been reported not to deteriorate in domains such as processing speed, visual memory, executive functioning, attention (Bora et al., 2013) and the extent of cognitive deficits at first-episode psychosis noted to be comparable to those at more chronic stages of schizophrenia (Sponheim et al., 2010). However, the rates of change over time in verbal working memory and verbal fluency have been noted to be different between controls and a first-episode psychosis sample (Bora et al., 2013). Previous research on the same first episode of psychosis cohort under investigation in the current thesis revealed that the
cognitive profiles of individuals with chronic schizophrenia were not significantly different from the magnitude of deficits at first episode presentation, with the exception of verbal learning which was significantly poorer in chronic schizophrenia (Schmidt, 2010). Deficits of processing speed also appeared more pronounced in chronic stages of the disorder although not significantly so. These findings could suggest that verbal learning and processing speed may be susceptible to further progressive deterioration over the course of illness, however being cross-sectional in nature the results of this comparison between first-episode and chronic cases can only be inferred. The longitudinal nature of the current thesis is optimal for further investigation of the course of verbal learning and processing speed deficits over time following a first psychotic episode.

**LIMITATIONS IN THE LITERATURE ON COGNITIVE COURSE IN SCHIZOPHRENIA**

In general, first-episode longitudinal studies examining selected cognitive domains are short in duration, typically less than five years later, with a few studies extending cognitive investigation up to ten years subsequent to the first-episode (Hoff et al., 2005; Oie et al., 2010). Meta-analyses have generally shown that further cognitive deterioration does not occur following a first psychotic episode (Bora et al., 2013). However, one main limitation in the literature is that there is uncertainty on the consensus regarding the long term trajectory of certain cognitive domains such as verbal learning and processing speed, with some research groups suggesting that they deteriorate further after a first psychotic episode, whereas others report stability or even an improvement. For example, verbal learning deficits were reported to remain stable over 3 years (Ayesa-Arriola et al., 2013), to deteriorate over 10 years and 13 years (Bozikas and Andreou, 2011, Øie et al., 2010); and to improve over 6 months and 2 years following an initial psychotic episode (Jahshan et al., 2010; Barder et al., 2013). Therefore, the current longitudinal study of cognition was carried out to elucidate the exact course of cognitive deficits following a first psychotic episode, in particular in aspects of cognition where uncertainty remains as to whether further deterioration occurs following the emergence of psychosis such as verbal learning and speed of processing.

A second limitation in the literature which the current thesis will address is the fact that a number of studies do not include a well-matched psychiatrically healthy control group when investigating the course of cognitive performance after a first psychotic episode. Significant changes in cognitive performance found over time in these studies cannot be definitively
attributed to the presence of a psychotic disorder. It is possible that any stability or improvement in performance in the psychosis group may not be genuine when compared to a matched control group; it is also possible that any decline in scores may be due to normal age-related cognitive changes. In general, studies including a control group report stability of deficits in executive functioning (Rodríguez-Sánchez et al., 2013; Ayesa-Arriola et al., 2013), working memory (Leeson et al., 2009; Ayesa-Arriola et al., 2013) and attention (Ayesa-Arriola et al., 2013), whereas speed of processing (Ayesa-Arriola et al., 2013) and verbal learning do not appear to remain stable following a psychotic episode (Rodríguez-Sánchez et al., 2013; Ayesa-Arriola et al., 2013), with some exception (Leeson et al., 2009, Bora et al., 2013). Studies investigating cognitive course after a psychotic episode without a control group are more susceptible to variability. Scores of verbal learning were found to increase over two years and subsequently return to baseline levels after 5 years (Barder et al., 2013) while others report no change in verbal learning over one year (Leeson et al., 2009). Similarly, variability in the reported trajectories of other cognitive abilities, compared to studies including a control group, is reported in working memory, logical memory and forward digit span, attention and logical deductive capabilities (Chang et al., 2014; Barder et al., 2013; Liu et al., 2011). As findings differ between studies with and without control groups, this highlights the need for including a well-matched control group in order to assign findings specifically to the disorder over time.

While not all studies adhere, some report the need to include baseline neuropsychology scores as a covariate in analyses of the longitudinal course of cognition as patient groups and controls are not matched for baseline scores. Ceiling effects may occur in controls limiting the extent of change possible over time while patients have more room to improve over time (Hoff et al., 1999; 2005). This research addresses this matter by covarying for baseline scores when assessing cognitive course after a first psychotic episode.

A final limitation in the literature is the lack of an accepted standard for measuring neuropsychological changes after first-episode psychosis (Nuechterlain et al., 2008). No common battery of cognitive tests is implemented throughout the literature. These methodological inconsistencies contribute to the difficulty in drawing consistent conclusion regarding cognitive profiles in psychosis and highlight the importance of implementing a specific test battery across a range of patient groups, locations and time-frames to thoroughly investigate the course of cognition in psychosis. One benefit of the current study is that we utilise the MATRICS Consensus Cognitive Battery (MCCB), a recommended battery
Thesis Introduction

for cognitive assessment in schizophrenia (Silverstein et al., 2010) to investigate cognitive course in psychosis.

Therefore, the current research will address these issues in the literature by implementing the MATRICS Consensus Cognitive Battery to identify the course of cognitive deficits after a first psychotic episode, in particular those areas of cognition where there is yet uncertainty as to whether further deterioration occurs after illness onset such as verbal learning and processing speed in a group of individuals with psychosis over time. Also, the inclusion of a well-matched psychiatrically healthy group for comparison and covarying for baseline neuropsychological scores will assist in drawing clearer conclusion about the nature of cognitive course in psychosis.

MATRICS CONSENSUS COGNITIVE BATTERY

The National Institute of Mental Health (NIMH) in the USA established the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) which yielded the validated MATRICS Consensus Cognitive Battery (MCCB) designed to identify the main separable cognitive impairments in schizophrenia and their alterations over time. While general cognitive deficits are apparent in schizophrenia, the MCCB examines seven separable dysfunctional cognitive factors that were replicable across studies and are seen as core elements of cognitive deficit in schizophrenia. These include speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition (see Paper 1, Table 3). Two of these cognitive domains in the MCCB (attention and working memory) correspond with the cognitive constructs of the NIMH Research Domain Criteria (RDoC), language is also included as well as an individual construct focusing on social systems (Cuthbert and Insel et al., 2010). It was anticipated that the identification of cognitive deficits using batteries such as the MCCB would be beneficial in the assessment of cognitive interventions and ultimately assist in improving long term functional outcome for patients (Green et al., 2004). The MCCB demonstrates excellent test-retest reliability and minimal practice effects (Roseberry & Kristian Hill, 2014; Nuechterlein et al., 2008). Of the few longitudinal first episode of psychosis studies that implemented the MCCB, Juuhl-Langseth et al. (2014) found that neurocognitive deficits were relatively stable over two years apart from the course of processing speed which showed a poorer course over time. By utilizing a robust, well established cognitive battery to assess cognitive profiles over time, the current thesis will provide a coherent reference for future studies which administer the MCCB to assess cognitive course in psychosis.
STRUCTURAL AND DIFFUSION MAGNETIC RESONANCE IMAGING

Another aspect of the current thesis involved investigations of the neuroanatomy of individuals with psychosis compared to controls in an effort to elucidate any structural anomalies that may be associated with cognitive deficits with marked poorer trajectories following illness onset. Identifying neuroimaging biomarkers identifying those most at risk of developing psychosis would benefit in early disease detection and targeted therapies (Kempton et al., 2015). Structural and diffusion magnetic resonance imaging (MRI) were employed to provide a comprehensive investigation of cortical and subcortical grey matter regions as well as white matter tracts of the brain. Structural T1-weighted images provide a high resolution image of grey and white matter regions of the brain and can be employed in investigations of structural abnormalities or pathologies of the brain in psychotic illness. However, due to the homogenous signal derived in white matter areas in T1-weighted images, diffusion-weighted MRI was employed to examine the orientational organization of white matter tracts of the brain. Diffusion MRI is based on diffusion properties of water molecules which are constrained by myelinated axons and provides a quantifiable measure of the orientation and degree of organization specific to a given tract of the brain. In the current thesis, all participants underwent structural and diffusion MR imaging in a 1.5 Tesla Siemens Magnetom Symphony scanner equipped with a 4-channel head coil. Structural data included acquiring a volumetric T1-weighted magnetization-prepared rapid acquisition of gradient echo (MPRAGE) sequence with this T1 image being utilized for studying the architecture of cortical regions such as volume, thickness and surface area and investigating volume of the whole brain. Diffusion data was acquired by applying whole brain high angular resolution diffusion imaging (HARDI) in 64 independent diffusion gradient directions. In previous literature, diffusion tensor imaging (DTI) was the established technique for characterising white matter microstructure with fractional anisotropy (FA) being the DTI-derived diffusion index of interest. However, this is an inadequate technique in regions of the brain with complex crossing fibres and introduces ambiguity in the reconstruction of white matter tracts (Jeurissen et al., 2013). In the current thesis, constrained spherical deconvolution (CSD) was utilized to estimate diffusion properties and reconstruct white matter tracts, which in contrast to tensor-based approaches takes into account crossing fibres and more complex fibre bundle arrangements. CSD enables white matter properties to be quantified using a tract-specific measure called hindrance modulated orientational anisotropy (HMOA) providing more accurate information regarding the microstructural
organisation of specific white matter tracts in all regions of the brain. The latter being applied herein allows us for the first time to examine the involvement of tracts in complex crossing fibre regions in cognitive outcomes.

While structural data was primarily employed for investigating grey matter regions of the brain and diffusion data for detailed investigation of white matter tracts of interest, both techniques were combined in investigations of brain networks or brain connectivity analyses. Network analysis is a novel method to study global inter-connectedness of the whole brain based on graph theory mathematics to describe the brain as a collection of nodes (grey matter regions) and edges (white matter tracts) (Rubinov et al., 2010; Friston, 1994). Topological measures of the brain are then investigated once the network is constructed, allowing the examination of brain integration, segregation and efficiency which are examined herein in relation to cognitive impairments in psychosis (Paper 3). Metrics used in the thesis included global characteristic pathlength (the average shortest pathlength of the brain network and a common measure of functional integration), global efficiency (the average inverse pathlength, lower average pathlengths are generally considered more efficient) and global nodal density (the number of edges of a network as a proportion of the total number of possible edges connecting the same number of nodes) (O’Donoghue et al., 2015; Sporns, 2011). Abnormalities in brain connectivity in schizophrenia have been reported using these metrics (Van den Heuval et al., 2010; Zalesky et al., 2011) supporting the disconnection hypothesis for schizophrenia (Friston, 1998) which states that aberrant connections between brain regions results in an inability to integrate neural information across distal brain regions and may underlie symptoms and cognitive impairments of the disorder (Stephan et al., 2006).

NEUROANATOMICAL CONTRIBUTIONS TO COGNITIVE DEFICITS

In a previous thesis which included the same first-episode dataset at a single time point, Schmidt (2010) examined the relationship between predefined local abnormalities and cognition in first-episode and a separately recruited group with chronic schizophrenia. Reduced grey matter volume in the caudate nuclei was reported at the time of first psychotic episode, however reduced volume did not explain impairments in overall cognitive performance in this group (Schmidt, 2010). Similarly, neuroanatomical abnormalities found in chronic psychosis, such as in the superior frontal gyrus, insulae and left caudate nucleus were not associated with overall cognitive deficits. However, this past thesis did not explore the relationship between brain abnormalities and separable cognitive domains of the MCCB investigated. Using the same FEP sample as Schmidt (2010), and in contrast to her focus on
investigating predetermined local brain abnormalities in relation to cognitive deficits, the current thesis investigated targeted brain regions and neural networks known to be involved in specific cognitive skills and examined if abnormalities therein explain the impairments experienced by individuals with psychosis. For example, the arcuate fasciculus language network was chosen to explore verbal cognitive deficits in this thesis. Global estimations of the brain were chosen to explore processing speed deficits due to the global operational nature of this cognitive skill. This approach may provide greater precision in uncovering abnormal neuroanatomical underpinnings of cognitive impairment in psychosis.

In contrast to the lack of relationship between brain abnormalities and cognitive deficits reported in Schmidt (2010), other studies have found relationships between executive functioning and Trail Making Test-A (psychomotor speed) and abnormalities in the fornix in schizophrenia (Knochel et al., 2016), where cortical connections between temporal lobe, frontal lobe and hippocampal formation may be altered and contribute to interference with normal cognitive functioning on this tasks. Additionally, at first episode, impairments in executive and motor functioning were associated with reductions of microstructural organisation of the major fasciculi connecting frontal and temporal regions and tracts connecting cortical to subcortical regions (Perez-Iglesias et al., 2010). Additionally, structural abnormalities in the left anterior hippocampus and orbito-frontal cortex have been linked to dysfunction in verbal performance and executive functioning in schizophrenia. Functional MRI studies, a hypofrontality or decreased cerebral blood flow in frontal brain regions has also been reported to occur in individuals with schizophrenia during cognitive task performance such as working memory (Carter et al., 1998). These studies highlight the role of a frontal-temporal network being involved in cognitive deficits in schizophrenia (Matsui et al., 2008). Hippocampal abnormalities have also been linked to verbal memory deficits in those at high risk for psychosis (Hurlemann et al., 2008).

Despite these findings, generally throughout the literature, linking cognitive deficits in the disorder to localised brain regions and circuitries has proven difficult and inconclusive. While lesion studies involving neuropsychological assessment can provide a tentative link between a specific cognitive ability and brain region the same has not been found for schizophrenia. Neurological cases cannot always be linked to neuropsychological performance in schizophrenia. However, some links may exist in the case of language impairments. Language abnormalities found in patients with frontal lobe lesions show similarities with the abnormal language features evident in schizophrenia (Alexander et al., 1989; Kaczmarek et al., 1987).
Thesis Introduction

It has been suggested that damage at any location of the many cortico-subcortical networks which connect with the prefrontal cortex may be related to the deficits of language in schizophrenia (Frith, 2014). However, the difficulty in linking neurological cases with the generalised cognitive deficits may be attributed to the heterogeneous nature of cognitive profiles in individuals with psychosis. Investigating the average performance of a varied group of individuals with psychosis does not provide a clear representation of the nature of cognitive impairment in the disorder and renders it difficult to link to neuroanatomy. Cognitive deficits in psychosis are broad and multifarious in nature each with its own underlying neural pathophysiology, contributing to the difficulty in determining core neural substrates and neuroanatomical mechanisms of cognitive dysfunction in schizophrenia. Some neural overlap may exist between certain related cognitive domains however. A common mechanism underlying deficits in working and episodic memory and context processing in schizophrenia may exist, with these three cognitive skills sharing impairments in the ability to represent goal directed information which guides behaviour (Barch et al., 2012). Abnormalities in the dorsolateral prefrontal cortex and its interaction with brain regions such as parietal cortex, thalamus and striatum, are suggested to underlie this proactive control as well as impairments in dopamine, GABA and glutamate neurotransmitters. However, as the underlying neuroanatomical mechanisms involved in differing cognitive domains are generally disparate to each other, examining specifically identified brain networks and systems involved in individual domains, as conducted in this thesis, is optimal. Modern structural and diffusion magnetic resonance imaging provides the potential to identify core neuroanatomical networks that are associated with specific cognitive impairment, thereby providing the potential to and further advance the traditional means of illness diagnosis through neuroanatomical biomarkers of cognitive deficits.

NOVEL ASPECTS OF THE THESIS

The knowledge gained in this research is original in nature. An important aspect of this study is that we investigated the course of cognitive deficits from time of first episode of psychosis, minimising confounds that arise in chronic schizophrenia such as chronicity of illness, medication use and institutionalization, enabling a more independent examination of longitudinal cognitive changes in psychosis. Investigations into the course of cognitive deficits after a first-episode of psychosis are pivotal as they can provide insight into any effect that a psychotic episode may have on the existing cognitive deficits. The neurotoxicity hypothesis suggested that the presence of psychosis expends a biological harmful effect on the brain and cognition (Wyatt, 1991). However, systematic reviews on this hypothesis have provided
incongruous findings with some in agreement with the hypothesis but the majority findings no toxicity effect (Rund, 2014). Therefore, further research into this is vital. This utilization of the MATRICS Consensus Cognitive Battery (MCCB) for neurocognitive profiling is also an important aspect of the study, as it is the recommended battery for cognitive assessment in schizophrenia (Silverstein et al., 2010). There is a lack of longitudinal studies which utilise the MATRICS battery to examine cognitive change in psychosis. By administering the MATRICS battery to this cohort, this study will provide a foundation for future longitudinal research to reference. In the current thesis, the neuroanatomical investigation of cognitive deficits in psychosis employed novel, cutting edge imaging techniques. A combination of structural and diffusion imaging was utilized in the analysis, optimizing the most relevant, up-to-date analytical strategies particularly in investigations of white matter tracts, network analysis of whole brain connectivity and overall analysis methodology.

**OVERALL THESIS AIMS**

Overall this study aimed to examine the trajectory of cognitive deficits after an initial psychotic episode and to identify neuroanatomical abnormalities that are associated with deficits in those cognitive domains which may be susceptible to further deterioration due to the presence of psychosis. These research goals were developed through three manuscripts embodied in this thesis (Papers 1, 2, and 3). Specific hypotheses are presented in detail in each paper respectively.

**Paper 1 Aim** – to investigate the longitudinal course of cognition over four years following a first psychotic episode. We hypothesised that in general, cognitive deficits present at the time of first-psychotic episode would remain stable and not deteriorate further, with the exception of certain cognitive domains with the most marked impairments, such as verbal learning, whose exact trajectory over illness course are uncertain in the current literature.

**Paper 2 Aim** – to investigate the microstructural organisation and lateralisation patterns of the arcuate fasciculus language related network in relation to verbal cognitive deficits in psychosis. The arcuate fasciculus was chosen due to its well established role in language in humans, and having being previously related to word learning in healthy individuals (Lopez-Barrauso et al., 2013). Lesions to the arcuate fasciculus network have also been linked to disorders of language such as conduction aphasia (Wernicke et al., 1987). Verbal learning and verbal fluency were included in this analysis due to their verbal elements, although verbal fluency is categorised under the cognitive domains of processing speed in the MATRICS
battery. We hypothesised that impaired white matter organisation in the arcuate fasciculus would relate to cognitive deficits in individuals with psychosis as well as a reduction of the normal left lateralisation patterns in these structures being associated with a psychotic disorder.

**Paper 3 Aim** – to examine the association between global brain characteristics and deficits in speed of processing in psychosis. Global estimations of the brain such as total brain volume and connectivity were chosen due to the global operational nature of processing speed conduction. Interhemispheric connections via the corpus callosum were also investigated as abnormalities in this tract have been consistently reported in schizophrenia (Pettersson-Yeo et al., 2011; Holleran et al., 2014) and previously related to processing speed impairments (Ajilore et al., 2015). We hypothesised that abnormalities in the connectivity of the brain on a global level and the efficiency of connections passing through the corpus callosum would be associated with deficits in speed of processing evident in individuals with psychosis.
REFERENCES


Thesis Introduction


Thesis Introduction


COGNITIVE COURSE IN FIRST-Episode Psychosis AND CLinical Correlates: A 4 Year Longitudinal Study Using The Matrics Consensus Cognitive Battery

Joanne Kenney¹, Heike Anderson-Schmidt², Cathy Scanlon¹, Sophia Arndt¹, Elisabeth Scherz¹, Shane Mclnerney¹,³, John McFarland³, Fintan Byrne¹, Mohamed Ahmed¹, Gary Donohoe⁵, Brian Hallahan¹, Colm McDonald¹, Dara M Cannon¹

¹Centre for Neuroimaging and Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine, Nursing and Health Sciences, National University of Ireland Galway, Galway, Ireland. ²Department of Psychiatry and Psychotherapy, University Medical Centre Goettingen, Georg-August University, Goettingen, Germany. ³Department of Psychiatry, St Michaels Hospital, Toronto, Canada. ⁴Department of Psychiatry, University of Toronto, Canada. ⁵Centre for Neuroimaging and Cognitive Genomics (NICOG), School of Psychology, National University of Ireland Galway, Galway, Ireland.

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ABSTRACT

**Background:** While cognitive impairments are prevalent in first-episode psychosis, the course of these deficits is not fully understood. Most deficits appear to remain stable, however there is uncertainty regarding the trajectory of specific cognitive domains after illness onset. This study investigates the longitudinal course of cognitive deficits four years after a first-episode of psychosis and the relationship of performance with clinical course and response to treatment.

**Methods:** Twenty three individuals with psychotic illness, matched with 21 healthy volunteers, were assessed using the MATRICS Consensus Cognitive Battery at illness onset and 4 years later. We also investigated the relationship between cognitive deficits and quality of life and clinical indices.

**Results:** Verbal learning and two measures of processing speed had marked poorer trajectory over four years compared to the remaining cognitive domains. Processing speed performance was found to contribute to the cognitive deficits in psychosis. Poorer clinical outcome was associated with greater deficits at illness onset in reasoning and problem solving and social cognition. Cognitive deficits did not predict quality of life at follow-up, nor did diagnosis subtype differentiate cognitive performance.

**Conclusion:** In conclusion, an initial psychotic episode may be associated with an additional cost on verbal learning and two measures of processing speed over a time spanning at least four years. Moreover, processing speed, which has been manipulated through intervention in previous studies, may represent a viable therapeutic target. Finally, cognition at illness onset may have a predictive capability of illness course.
INTRODUCTION

Deficits in many areas of cognition are prevalent in individuals who experience a first-episode of psychosis (FEP), many of which are also present in the prodromal phase of psychosis. Visual memory, verbal learning, attention, working memory, executive function and social cognition are common cognitive domains impaired in FEP compared to the performance of healthy controls (Bora et al., 2014, Aas et al., 2014, Üçok et al., 2013). It is important to elucidate the trajectory of cognitive dysfunction following an initial psychotic episode, and any clinical or biological determinants of such progression, which can only be established by longitudinal studies of cognitive function.

In general, it has been shown that the majority of cognitive deficits remain stable following an initial psychotic episode (Bozikas and Andreou, 2011; Bora and Murray, 2013), although there is variability throughout the literature. For example, verbal learning has variously been reported to either remain stable over 3 years (Ayesa-Arriola et al., 2013), to deteriorate over 10 years and 13 years (Bozikas and Andreou, 2011, Øie et al., 2010); or to improve over 6 months and 2 years (Jahshan et al., 2010; Barder et al., 2013). A table of recent longitudinal studies, consisting of studies additional to the meta-analysis by Bora and Murray (2013) is provided in Table 1.

The heterogeneity of results in the literature may partly relate to the lack of a congruent set of cognitive tests administered to assess cognitive performance, which also restricts comparison of findings across studies. Measuring performance of a cognitive construct using alternative tests can result in incongruent findings (Liu et al., 2011). The current study aimed to address this issue by implementing the MATRICS Consensus Cognitive Battery (MCCB), which was developed by the National Institute of Mental Health’s (NIMH) Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). The MCCB identified seven separable dysfunctional cognitive factors in the disorder, two of which (attention and working memory) are concurrent with the cognitive constructs of the NIMH Research Domain Criteria (RDoC) (Cuthbert and Insel, 2010).

The MCCB demonstrates excellent test-retest reliability and minimal practice effects (Roseberry and Kristian Hill, 2014, Nuechterlein et al., 2008). Of the few FEP longitudinal studies that implemented the MCCB, Juuhl-Langseth et al. (2014) found that most neurocognitive deficits were relatively stable over two years apart from the course of processing speed.
The current study additionally sought to investigate the relationship between cognitive deficits in psychosis and other clinical and quality of life measures as the nature of these relationships remain inconclusive. In terms of clinical symptomatology, cognitive deficits are proposed to be more closely associated with negative and disorganised aspects of psychosis compared with positive symptoms (Bora and Murray, 2013; Domínguez et al., 2009). Attention, psychomotor speed and verbal learning in particular have been found to correlate with negative symptoms in schizophrenia (August et al., 2012; Bora and Murray, 2013; O’Gráda et al., 2009), while disorganised symptoms were related to lower verbal and visual learning, processing speed and social cognition (August et al., 2012; Flaum et al., 2000). Whether or not cognitive performance differs significantly between subtypes of psychosis, such as affective and non-affective subtypes, has not been determined conclusively. Some evidence has suggested verbal learning performance to differ between individuals with schizophrenia from those with affective disorders (Fitzgerald et al., 2004) but this is not a consistent finding (Bora et al., 2009). Finally, longitudinal associations between cognitive deficits and quality of life outcome in schizophrenia have been supported by a review of 18 studies (Green et al., 2004), albeit with considerable variability (Tolman et al., 2010).

This study aims to characterise the longitudinal course of cognitive deficits four years after a first episode of psychosis using the standardised MCCB, to determine the nature and degree of variation in cognitive performance and critically, to examine the relationship of performance with clinical course and response to treatment.
Table 1. Recent longitudinal studies examining cognitive change across the course of psychosis from the first episode (shaded rows indicate studies with repeated testing of healthy control group included)

<table>
<thead>
<tr>
<th>Study</th>
<th>Group (n)</th>
<th>Follow-up</th>
<th>Age at baseline</th>
<th>Cognitive Domain (Cognitive Tests)*</th>
<th>Significant findings for each domain/test</th>
<th>Medication Effect</th>
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</thead>
<tbody>
<tr>
<td>Chang (2014)</td>
<td>FES (n=93); no HC</td>
<td>3 years</td>
<td>31±10</td>
<td>Logical memory - WMS-R</td>
<td>∆FES ↑ ∆FES ↑ ∆FES ↑ ∆FES ↔ ∆FES ↑</td>
<td>No information given</td>
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<td>Visual reproduction test -WMS-R</td>
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<td>Forward digit span -WAIS-R</td>
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<td>Category verbal fluency</td>
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<td>Modified WCST</td>
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<tr>
<td>Rodriquez-Sanchez (2013)</td>
<td>FEP non-affective (n=78), HC (n=43)</td>
<td>1, 3 years</td>
<td>FE (29 ± 9); HC (28± 8)</td>
<td>Verbal memory (RAVLT)</td>
<td>∆FEP&lt;∆HC ∆FEP&lt;∆HC ∆FEP↔∆HC ∆FEP↔∆HC</td>
<td>No information given</td>
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<td>Visual memory (RCFT)</td>
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<td>Motor dexterity (grooved pegboard)</td>
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<td>EF-SOP (TMT A and B, WAIS III-BD + DS)</td>
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<td>Attention (CPT-DS – total score + BTA)</td>
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<td>Impulsivity (CPT-DS – EOC)</td>
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<tr>
<td>Ayesa-Arriola (2013)</td>
<td>FES (n = 79); randomised to 3 groups: haloperidol; olanzapine; risperidone; HC (n=41)</td>
<td>6 mths, 1 year, 3 years</td>
<td>haloperidol (27±7 yrs); olanzapine (27±8 yrs); risperidone (28±9 yrs); controls (28±8 yrs)</td>
<td>Verbal memory (RAVLT)</td>
<td>∆FES (haloperidol + olanzapine)&lt;∆HC ∆FES (haloperidol)&lt;∆HC ∆FES↔∆HC ∆FES↔∆HC</td>
<td>Randomised into 3 treatment groups: Verbal learning + decision making: - ∆olanzapine&gt;∆haloperidol; SOP: - ∆olanzapine&gt;∆risperidone</td>
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<td>Visual memory (RCFT)</td>
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<td>Motor coordination (grooved pegboard)</td>
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<td>EF (TMT-B and FAS)</td>
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<td>Working memory (WAIS-III-BD)</td>
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<td>Speed of processing (WAIS-III-DS)</td>
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<td>Attention (CPT-DS)</td>
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<td>Decision-making capacity (IOWA gambling task)</td>
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</tbody>
</table>
### Legend

- **FEP**: first-episode psychosis
- **FES**: first-episode schizophrenia
- **HC**: healthy controls
- **EOS**: early-onset schizophrenia
- **∆FEP**: rate of change in scores over time in the FEP group
- **∆HC**: rate of change in scores over time in the HC group
- **FEP<HC**: less improvement in rate of change of scores over time in FEP group compared to HC group
- **FEP>HC**: greater improvement in rate of change of scores over time in FEP group compared to HC group
- **FEP↔HC**: no difference in rate of change between groups (stability)
- **↑**: increase in score over time
- **↓**: decrease in scores over time
- ** ↔**: no significant change in score over time

### Table

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Age Range</th>
<th>Timepoints</th>
<th>Cognitive Domains</th>
<th>ΔFEP</th>
<th>ΔFW</th>
<th>ΔFHC</th>
<th>ΔFEC</th>
<th>ΔFES</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barder (2013)</td>
<td>FEP(n = 62); No HC</td>
<td>28 ± 9 yrs</td>
<td>1, 2 and 5 years</td>
<td>Verbal learning (CVLT) Motor-speed index (FFT) EF (WCST) Working memory (COWA, digit span, CPT-IP hits) Impulsivity (CPT-IP RT + FA)</td>
<td>ΔFEP ↑ 2 yrs, ↓ 5 yrs ΔFEP ↔ 2 yrs, ↔ 5 yrs After controlling for medication, all key findings remained significant.</td>
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<td>Liu (2011)</td>
<td>FES (n = 31); no HC</td>
<td>28 ± 10 yrs</td>
<td>1 year, 3 year</td>
<td>EF: Modified SET + Modified WCST</td>
<td>ΔFEP ↔ ΔFEP ↑</td>
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<tr>
<td>Popolo (2010)</td>
<td>FEP (n = 15); no HC</td>
<td>22.9 ± 2.9 yrs</td>
<td>1 year</td>
<td>Verbal learning (RAVLT) Attention (SSA + SAM) Semantic-lexical memory (FAS) Logical deductive capabilities (CPM) Flexibility + Problem solving (WCST)</td>
<td>ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ ΔFEP ↔ No information given</td>
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<tr>
<td>Leeson (2009)</td>
<td>FEP(n = 60); HC (n = 27)</td>
<td>FEP (Low IQ = 24±7), deteriorated IQ 25±8, preserved IQ 27±9; HC 27±7</td>
<td>3 years</td>
<td>Verbal learning (RAVLT) CANTAB: Working memory (SS + SWM) Planning (TOL)</td>
<td>ΔFEP ↔ ΔHC ΔFEP ↔ ΔHC ΔFEP ↔ ΔHC ΔFEP ↔ ΔHC No information given</td>
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</table>

*Where cognitive domains not explicitly stated, cognitive tests presented only

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**Note:**
- ΔFEP, rate of change in scores over time in the FEP group
- ΔHC, rate of change in scores over time in the HC group
- FEP<HC, less improvement in rate of change of scores over time in FEP group compared to HC group
- FEP>HC, greater improvement in rate of change of scores over time in FEP group compared to HC group
- FEP↔HC, no difference in rate of change between groups (stability)
- ↑ increase in score over time
- ↓ decrease in scores over time
- ↔no significant change in score over time

**Cognitive Tests:**
- CVLT: California Verbal Learning Test
- FFT: Fast Forgetting Test
- WCST: Wisconsin Card Sorting Test
- COWA: Controlled Oral Word Association Test
- CPT-IP: Continuous Performance Test-Identical Pairs
- SSA: Span Selection Attention
- SAM: Spinnler Attention Matrices
- CPM: Coloured Progressive Matrices
- TOL: Tower of London Task
- CT: Category Fluency
- SC: Symbol Coding
- MSCEIT: Mayer–Salovey–Caruso Emotional Intelligence Test
- RAVLT: Rey Auditory Verbal Learning Test
- RCFT: Rey Complex Figure Test
- BD: Backward Digits
- DS: Digit Symbol
- SS: Spatial Span
- SWM: Spatial Working Memory
- CPT-DS: Continuous Performance Test-Degraded Stimulus
- EOC: total number of corrections of errors of commission
- BTA: Brief Test of Attention
- Modified SET: Six Elements Test
- KRFT: Kimura Recurring Figure Test
- WMS: Weschler Memory Scale
- WAIS: Weschler Adult Intelligence Scale
- WCST: Wisconsin Card Sorting Test
- CF: Category Fluency
- SC: Symbol Coding
METHODS AND MATERIALS

Participants

Initially, 36 individuals who experienced a first episode of psychosis (FEP) and 59 healthy non-psychotic were from the mental health services at University Hospital Galway and the surrounding mental health services in the west of Ireland. All subjects were aged between 18-49 years at baseline (Table 2). The recruitment and clinical assessment of these individuals is described previously (McFarland et al., 2013; Scanlon et al., 2014). Exclusion criteria for both groups were as follows: a history of neurological disorders (including epilepsy), comorbid substance or alcohol abuse in the last year, a history of head injury resulting in loss of consciousness for over 5 minutes, a history of oral steroid use in the previous three months, loss of weight in excess of 12% of the original body weight in the previous year and a history of viral infection in previous 1 month. Individuals in the control group were also excluded if there was a personal or family history of psychotic or affective disorder. Written informed consent was obtained from all participants. The study was approved by the research Ethics Committees of the National University of Ireland Galway and Galway University Hospitals.

At follow-up, on average four years later (4.3±0.9 years), 23 FEP and 21 HC subjects were successfully re-recruited. Two individuals from the original cohort were un-contactable, 1 individual was unwell, 8 individuals declined the invitation to participate and 2 had relocated to another country. Many individuals in the control group had also relocated making it difficult to re-recruit in that cohort. There was no significant difference in the mean age, gender or baseline diagnosis of individuals from the original cohort who were successfully recruited at follow-up compared to those not recruited.
**Table 2.** Demographic Characteristics of the study sample

<table>
<thead>
<tr>
<th></th>
<th>FEP group</th>
<th>HC group</th>
<th>Comparison (T/χ²,p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline N</td>
<td>37</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Follow-up N</td>
<td>23</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Attrition Rate %</td>
<td>38%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Age at onset (mean yrs±SD)</td>
<td>24.8±8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Baseline (mean yrs±SD)</td>
<td>28.3±7.7</td>
<td>29.0±7.7</td>
<td>0.3,0.8</td>
</tr>
<tr>
<td>Gender N (% fem) (ratio)</td>
<td>15, 8 (35%) (1.88:1)</td>
<td>13, 8 (38%) (1.63:1)</td>
<td>0.05, 0.8</td>
</tr>
<tr>
<td>NART (mean score±SD)</td>
<td>112.7±7.6</td>
<td>115.2±6.6</td>
<td>1.2, 0.3</td>
</tr>
<tr>
<td>Education (mean years±SD)</td>
<td>15.8±3.2</td>
<td>18.1±2.7</td>
<td>2.6, 0.012*</td>
</tr>
<tr>
<td>Time between testing (mean years±SD)</td>
<td>4.65±0.81</td>
<td>3.86±0.79</td>
<td>-3.3, 0.002*</td>
</tr>
</tbody>
</table>

**Legend.** FEP = first episode psychosis; HC = healthy control; NART = national adult reading test; N = sample number; FU = follow-up; * = significant difference

**Cognitive Measures**

The MCCB was administered to individuals at the time of their first psychotic episode and to a psychiatrically healthy control group. Follow-up testing was completed four years later. A summary of the seven cognitive domains which constitute the MCCB can be found in Table 3.
Table 3. The seven cognitive domains which constitute the MCCB and a description of their respective tests.

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Cognitive Tests</th>
<th>Description of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of Processing</td>
<td>Trail Making Test (TMT): Part A</td>
<td>a test of visual scanning and visuomotor tracking</td>
</tr>
<tr>
<td></td>
<td>Brief assessment of Cognition in Schizophrenia (BACS)</td>
<td>primarily a measure of visuomotor speed</td>
</tr>
<tr>
<td></td>
<td>Category Fluency: Animal Fluency</td>
<td>a verbal index of speed of processing</td>
</tr>
<tr>
<td>Attention/Vigilance</td>
<td>Continuous Performance Test – Identical Pairs (CPT-IP)</td>
<td>a measure of attention or vigilance (Cornblatt et al., 1989)</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Wechsler Memory Scale (WMS*-III): Spatial Span forward and backward (WMS-SS)</td>
<td>a measure of nonverbal working memory</td>
</tr>
<tr>
<td></td>
<td>Letter number span (LNS)</td>
<td>a test of verbal working memory including maintenance and manipulation of components of working memory</td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>Hopkins Verbal Learning Test – Revised (HVLTR)</td>
<td>a list of 12 words presented 3 times, which must be recalled from memory</td>
</tr>
<tr>
<td>Visual Learning</td>
<td>Brief Visuospatial Memory Test-Revised (BVMT-R)</td>
<td>the participant is required to draw 6 geometrical figures as accurately as possible from memory</td>
</tr>
<tr>
<td>Reasoning &amp; Problem Solving</td>
<td>Neuropsychological Assessment Battery (NAB): Mazes</td>
<td>this test involves planning and foresight which are elements of reasoning and problem solving</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT): Managing Emotions</td>
<td>this test measures how well people solve emotional problems (Mayer et al., 2003)</td>
</tr>
</tbody>
</table>

Clinical Assessment

The severity of symptoms in the FEP group were clinically assessed by a trained psychiatrist at both time points using the Positive and Negative Syndrome Scale (PANSS) (Kay and Qpjer, 1982) and the Structured Clinical Interview for DSM-IV Research Version (American Psychiatric Association, 2000). The Quality of Life Scale (QLS) was administered (Heinrichs et al., 1984) at follow-up. Total antipsychotic medication taken was recorded and converted to chlorpromazine (CPZ) equivalents (Lehman and Steinwachs, 1998; Woods, 2003).

To assess whether affective and non-affective subtypes present differentially, diagnoses at follow-up were categorised into two groups. Schizophrenia (n=6), schizophreniform
disorder (n=1), schizoaffective disorder (n=3), psychotic disorder not otherwise specified (4) and delusional disorder (n=1) were defined as non-affective types of psychoses whereas bipolar I disorder (n=6) and major depressive disorder, recurrent (n=2) defined as affective types of psychoses (Table 4).

Table 4. Clinical features at illness onset and follow-up of study sample who were successfully recruited after 4 years (n =23)

<table>
<thead>
<tr>
<th>Duration of Untreated Psychosis (months)</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Comparison (t/Z,p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bipolar I disorder</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder, recurrent</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Symptoms levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS positive score</td>
<td>17±5</td>
<td>10±4</td>
<td>-3.5, &lt;0.001*†</td>
</tr>
<tr>
<td>PANSS negative score</td>
<td>14±6</td>
<td>12±7</td>
<td>-1.2, 0.30†</td>
</tr>
<tr>
<td>PANSS general score</td>
<td>31±15</td>
<td>23±6</td>
<td>4.7, &lt;0.001*</td>
</tr>
<tr>
<td>PANSS total score</td>
<td>62±11</td>
<td>45±15</td>
<td>-3.5, 0.001*†</td>
</tr>
<tr>
<td>Functionality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Assessment of Functioning</td>
<td>53±10</td>
<td>69±22</td>
<td>-3.2, 0.001*†</td>
</tr>
<tr>
<td>Medication at FU (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood stabilisers</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing information</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalent</td>
<td>159±268</td>
<td>204±224</td>
<td>-1.1, 0.266†</td>
</tr>
<tr>
<td>Usual Symptom Severity at FU (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No further episodes</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing information</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis Type (SCID)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-affective</td>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Affective</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Legend. N = sample number; PANSS = Positive and Negative Syndrome Scale; FU = follow-up; SCID = Structured Clinical Interview for DSM. * = significant difference between baseline and follow-up values; † = non-normal distribution (Wilcoxon Rank Test used)
Statistics

Raw scores of the cognitive tests were age and gender corrected using the MCCB computerised program, and converted to T-scores, which were then used in all subsequent statistical analyses. Normative data were obtained from administering the battery to 300 individuals across five sites in the U.S. (Kern et al., 2008) stratified into three age ranges and accounting for gender and education. All statistics were conducted using IBM SPSS (v.21). Shapiro-Wilk tests were used to test for normal distribution of each cognitive variable. Most cognitive variables at onset of psychosis were normally distributed (W=0.94-0.99, p=0.19-0.93) except for attention (W=0.96, p=0.006), visual learning (W=0.94, p<0.001), speed of processing (W=0.97, p=0.04) and the composite cognition score (W=0.97, p=0.03). All cognitive measures were normally distributed at follow-up (W=0.92-0.98, p=0.08-0.90) apart from the composite cognitive score (W=0.93, p=0.01). ANOVA models were used to compare group differences in cognitive performance at both time points and the Kruskal-Wallis test was used for the non-normally distributed measures.

Cognitive change variables (scores at follow-up minus those at baseline of each cognitive test) were tested for normality of distribution. Positive cognitive change values indicated improvement in performance over time; negative values indicated a decrease over time. Most measures did not deviate from a normal distribution (W=0.94-0.98, p=0.11-0.92), with the exception of a measure of working memory, the spatial span test (W=0.94, p=0.02). This test was transformed for normal distribution using square root transformation (W=0.95, p=0.08) to allow covariates to be accounted for in an ANCOVA model. ANCOVA models with each cognitive change variable were analysed with baseline cognitive scores and years of education included as covariates.

When investigating the longitudinal relationship between any cognitive change variables with significant group differences and clinical and quality of life variables, Pearson’s correlation analyses (r) and regression models were used. Non-parametric tests such as Spearman’s correlation (ρ) were used with non-normally distributed clinical variables.
RESULTS

Healthy controls (HC) performed significantly better than individuals experiencing their first episode of psychosis (FEP) on all measures of cognition at baseline and follow-up, the only exception being social cognition scores at follow-up where no group difference was found (Table 5).

Table 5. Baseline and follow-up (FU) cognitive scores of FEP group and healthy controls on the seven cognitive domains of the MCCB

<table>
<thead>
<tr>
<th>Cognitive Domains</th>
<th>Baseline</th>
<th></th>
<th>Follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEP(n=37)</td>
<td>HC(n=59)</td>
<td>%Difference</td>
<td>FEP(n=23)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Speed of Processing</td>
<td>36±13 †</td>
<td>59±11 †</td>
<td>-29%*</td>
<td>38±14</td>
</tr>
<tr>
<td>Attention/Vigilance</td>
<td>39±13 †</td>
<td>48±8 †</td>
<td>-21%*</td>
<td>44±13</td>
</tr>
<tr>
<td>Working Memory</td>
<td>38±10</td>
<td>48±8</td>
<td>-21%*</td>
<td>43±13</td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>40±9</td>
<td>46±10</td>
<td>-28%*</td>
<td>44±10</td>
</tr>
<tr>
<td>Visual Learning</td>
<td>40±14 †</td>
<td>51±11 †</td>
<td>-31%*</td>
<td>41±14</td>
</tr>
<tr>
<td>Reasoning/Problem Solving</td>
<td>38±8</td>
<td>50±10</td>
<td>-22%*</td>
<td>42±9</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>43±16</td>
<td>55±9</td>
<td>-22%*</td>
<td>48±13</td>
</tr>
<tr>
<td>Total Cognition</td>
<td>32±13 †</td>
<td>50±10 †</td>
<td>-30%*</td>
<td>39±15 †</td>
</tr>
</tbody>
</table>

Legend. FEP = first episode psychosis; HC = healthy controls; † median used where non-normal distribution; *** p< 0.001 ** p< 0.01 *p < 0.05; % difference = percentage difference of FEP scores relative to HC scores

A significant group difference was found between the FEP group and controls on the change in performance over time on a visuomotor test of processing speed, the Trail Making Test and a verbal index of processing speed, the Verbal Fluency test. A significant group difference was also found on the change in verbal learning performance over time (Table 6; Figure 1).

There was no significant group difference in the change in performance on the remaining cognitive metrics (Table 6). The results remained similar without covarying for years of education or when the NART (National Adult Reading Test; Nelson et al., 1991) was covaried in place of years of education (Table 6). Similarly, the magnitude and direction of the findings remained the same when time between testing was additionally covaried for (Table 2).

Results also remained similar when patients on no medication were removed from analysis (n=8), however, there was an additional significant group difference in the composite speed of processing score between this subgroup of FEP individuals taking medication and healthy controls (p=0.02;FEP(m±se)= -
4.42±2.4, HC=4.3±1.9). Total chlorpromazine equivalents were not related to those cognitive measures found to have significant group differences (p=-0.3 -0.1, p=0.1-0.6).

Table 6. Change in scores over time on the cognitive domains and separable cognitive tests of the MCCB

<table>
<thead>
<tr>
<th>Tests</th>
<th>FEP change</th>
<th>HC change</th>
<th>CI 95%</th>
<th>F (†)</th>
<th>P(†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of Processing</td>
<td>-0.66±2.14</td>
<td>4.82±2.27</td>
<td>[-1.8,12.8]</td>
<td>2.31(2.94)</td>
<td>0.14(0.09)</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td>-2.94±2.5</td>
<td>5.56±2.62</td>
<td>[0.4,16.61]</td>
<td>4.49(5.5)</td>
<td>0.04*(0.02)</td>
</tr>
<tr>
<td>BACS:SC</td>
<td>1.84±1.9</td>
<td>0.23±2.06</td>
<td>[-8.3,5.03]</td>
<td>0.24(0.09)</td>
<td>0.63(0.93)</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>-2.94±2.4</td>
<td>8.23±2.5</td>
<td>[3.56,18.8]</td>
<td>8.81(7.21)</td>
<td>0.005*(0.01)</td>
</tr>
<tr>
<td>Attention/Vigilance</td>
<td>1.45±1.7</td>
<td>2.58±1.85</td>
<td>[-4.34,6.6]</td>
<td>0.17(0.04)</td>
<td>0.68(0.85)</td>
</tr>
<tr>
<td>Working Memory</td>
<td>4.26±1.83</td>
<td>6.71±1.94</td>
<td>[-3.4,8.4]</td>
<td>0.70(0.41)</td>
<td>0.41(0.53)</td>
</tr>
<tr>
<td>WMS: Spatial Span</td>
<td>4.82±0.19</td>
<td>5.24±0.21</td>
<td>[-0.2,1.05]</td>
<td>1.74(0.71)</td>
<td>0.19(0.40)</td>
</tr>
<tr>
<td>Letter Number</td>
<td>3.85±2.01</td>
<td>6.16±2.11</td>
<td>[-4.0,6.6]</td>
<td>0.55(0.42)</td>
<td>0.46(0.52)</td>
</tr>
<tr>
<td>Span</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>2.0±1.8</td>
<td>9.28±1.88</td>
<td>[1.67,12.9]</td>
<td>6.86(5.58)</td>
<td>0.01*(0.02)</td>
</tr>
<tr>
<td>Visual Learning</td>
<td>-0.09±2.04</td>
<td>1.81±2.15</td>
<td>[-4.5,8.3]</td>
<td>0.36(0.49)</td>
<td>0.05(0.48)</td>
</tr>
<tr>
<td>Reasoning</td>
<td>1.52±2.07</td>
<td>5.28±2.19</td>
<td>[-3.1,10.6]</td>
<td>1.25(1.25)</td>
<td>0.27(0.27)</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>2.87±1.99</td>
<td>-1.0±2.04</td>
<td>[-10.1,2.4]</td>
<td>1.55(0.48)</td>
<td>0.22(0.49)</td>
</tr>
<tr>
<td>Total Cognition</td>
<td>4.24±1.64</td>
<td>4.83±1.75</td>
<td>[-4.9,16.7]</td>
<td>0.05(0.04)</td>
<td>0.83(0.85)</td>
</tr>
</tbody>
</table>

Legend. Adjusted means ± standard error reported; FEP = first episode psychosis; HC = healthy controls; CI = 95% confidence intervals; BASC:SC = Brief assessment of Cognition in Schizophrenia: Symbol Coding; WMS = Working memory scale; *significant group difference; (†) F and p values when years of education omitted as covariate.
In the FEP group, the change in cognitive performance on the visuospatial and verbal index of processing speed or verbal learning was not related to the change in clinical symptom profile, positive ($r$=-0.2-0.2, $p$=0.4-0.8) or negative ($r$=-0.1-0.4, $p$=0.1-0.6) symptoms on the PANSS. Diagnosis subtype (affective vs. non affective) did not significantly differentiate cognitive performance on these measures ($F$=0.05-4.1, $p$=0.1-0.8). Reasoning and problem solving (Beta=-0.48, $p$=0.004) and social cognition (Beta=-0.31, $p$=0.001) at onset of psychosis significantly predicted negative symptoms severity at follow-up ($F$=12.54, $p$<0.001, Figure 2). No cognitive tests at illness onset related to severity of positive symptoms four years later ($r$=-0.15-0.26, $p$=0.25-0.98) or quality of life at follow-up ($r$=0.03-0.38, $p$=0.09-0.89).
Figure 2. Capacity for social cognition and reasoning and problem solving at onset of illness to predict the severity of negative symptoms four years later.

Post-hoc analyses were conducted to determine the extent of the influence processing speed and verbal learning had on other cognitive domains. After controlling for processing speed on cognitive scores at illness onset and follow-up (Table 6), group differences on cognitive measures decreased substantially and many became non-significant (average % decrease in F value of both time points was 82%). When covarying for verbal learning, group differences on more cognitive tests remained significant although F values moderately decreased (average % decrease in F value was 56%, Table 7).
Table 7. Post-hoc analysis of group differences with and without covarying for speed of processing and verbal learning

<table>
<thead>
<tr>
<th>Tests</th>
<th>Baseline (n = 37)</th>
<th>Follow-up (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before covarying</td>
<td>After covary for SOP</td>
</tr>
<tr>
<td></td>
<td>F, p</td>
<td>% diff</td>
</tr>
<tr>
<td>Speed of Processing</td>
<td>43.07, &lt;0.001*</td>
<td>25.29, &lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>1.54, 0.22</td>
<td>-41%</td>
</tr>
<tr>
<td>Attention/Vigilance</td>
<td>21.18, &lt;0.001*</td>
<td>10.82, 0.001*</td>
</tr>
<tr>
<td></td>
<td>2.76, 0.11</td>
<td>-49%</td>
</tr>
<tr>
<td>Working Memory</td>
<td>24.97, &lt;0.001*</td>
<td>9.65, 0.003*</td>
</tr>
<tr>
<td></td>
<td>8.54, 0.004*</td>
<td>-61%</td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>23.32, &lt;0.001*</td>
<td>5.97, 0.02*</td>
</tr>
<tr>
<td></td>
<td>3.72, 0.06</td>
<td>-68%</td>
</tr>
<tr>
<td>Visual Learning</td>
<td>18.58, &lt;0.001*</td>
<td>5.97, 0.02*</td>
</tr>
<tr>
<td>Reasoning</td>
<td>30.02, &lt;0.001*</td>
<td>17.92, &lt;0.001*</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>12.54, 0.001*</td>
<td>6.33, 0.01*</td>
</tr>
<tr>
<td>Total Cognition</td>
<td>56.03, &lt;0.001*</td>
<td>26.72, &lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>10.04, 0.002*</td>
<td>-52%</td>
</tr>
</tbody>
</table>

Legend. % diff = percentage decrease (-) in F scores following covarying; SOP = speed of processing; VL = verbal learning; * = significant group difference
DISCUSSION

Longitudinal cognitive performance remained significantly poorer over the four years following a first-episode of psychosis relative to psychiatrically healthy controls (Table 5). Two measures of speed of processing, the Trail Making Test and Verbal Fluency test, showed a significant reduction in performance over time, whereas verbal learning displayed a reduced rate of improvement over time, compared to other domains which improved at the same rate as controls (Table 6; Figure 1). These data suggest that the initial psychotic episode may be associated with an additional cost on a person’s cognitive course in these domains over a time spanning at least four years. Secondly, processing speed performance accounted for a considerable amount of variance in the impairments of the other cognitive domains. Finally, poorer clinical outcome, specifically negative symptoms, was associated with greater deficits at illness onset in reasoning and problem solving and social cognition.

The comprehensive deficits in cognitive capacity in individuals with psychosis are consistent with the literature, specifically a reduced improvement in processing speed and verbal learning over time relative to other cognitive domains has previously been reported (Juuhl-Langseth et al., 2014; Rodríguez-Sánchez et al., 2013; Bozikas and Andreou, 2011), although not uniformly (Leeson et al., 2009). Stability in the remaining cognitive deficits has also been identified in measures of attention (Rodríguez-Sánchez et al., 2013; Ayesa-Arriola et al., 2013) social cognition (Horan et al., 2012) working memory (Ayesa-Arriola et al., 2013; de Mello Ayres et al., 2010) reasoning and problem solving (Juuhl-Langseth et al., 2014) and visual learning (Ayesa-Arriola et al., 2013).

While a broad array of symptoms and deficits in ability contribute to real world disability in schizophrenia, cognition in particular has been identified as a determinant of quality of life. While the current study found no relationship between cognitive deficits in psychosis and quality of life outcome, this may be the result of poor statistical sensitivity or due to the use of the Heinrich’s quality of life scale which includes both objective and subjective measures, the latter being associated less with cognition (Tolman et al., 2010).

As two measures of speed of processing demonstrated reduced performance over time in psychosis, post-hoc analysis additionally examined the processing speed hypothesis, which proposes that slower performance on this measure reduces the ability to process information automatically and effectively and contributes to the deficits in a wide array of
cognitive skills (Kelleher et al., 2013; Rodríguez-Sánchez et al., 2007). In our study, processing speed appeared to play a significant role in the impairment in other cognitive measures such as working memory and attention. Future studies may specifically investigate the impact of cognitive remediation on processing speed for individuals experiencing a first psychotic episode and whether performance on other cognitive domains benefits as a result.

The relationship between cognition and negative symptoms in first episode psychosis and schizophrenia has been well replicated by many groups (Bora and Murray, 2013, Lam et al., 2014) if not all (Hoff et al., 1999). When investigating the clinical relevance of our cognitive findings we found poorer cognitive ability, specifically reasoning and problem solving and social cognition at illness onset, to predict greater negative symptom severity four years later. Longitudinally, performance on a variety of cognition domains at illness onset, such as processing speed, IQ, working memory and verbal learning, have been found to relate to the course of negative symptom severity (Leeson et al., 2010; Carlsson et al., 2006; Bora and Murray, 2013; González-Ortega et al., 2013). Taken together, these data support cognition at illness onset as a potential predictive indicator of illness course; however, there is yet heterogeneity as to which exact cognitive domain which relates to negative symptom severity.

At follow-up, no deficit in social cognition was evident in the individuals who experienced a psychotic episode, potentially due to the possibility of a baseline ceiling effect in the control group. Despite the absence of a deficit in social cognition at follow-up relative to onset, these data do not definitively support a normalisation in this domain. During and following establishment of the MATRICS battery the sensitivity and specificity of the social cognition domain has repeatedly been questioned, and its relationship to other cognitive domains and other social cognition measures remains uncertain (Pinkham, 2014). In light of compelling evidence of social cognition deficits among patients with chronic schizophrenia, the failure to observe the expected differences between individuals with psychosis and controls at follow-up leads us to recommend this be explicitly examined in future longitudinal studies.

On nearly all measures, there was a tendency for all participants to score more highly at the second time point, consistent with the existing literature (Bora and Murray, 2013; Rodríguez-Sánchez et al., 2013). The MCCB has been shown to have minimal practice effects, reducing the likelihood that these improvements reflect practice effects. The young
mean age of the sample in this study may have contributed to the improvement in longitudinal cognitive scores, perhaps a reflection of further brain development or education.

A strength of the current study is the well characterised longitudinal sample which is likely to be representative of the first-episode psychosis population. The sample was relatively heterogeneous compared to a sample of first episode schizophrenia, although post-hoc analysis did not identify differences between affective and non-affective subtypes which may contribute positively to the generalisability of the findings to the population. Use of the standardised neurocognitive battery also enables compatible comparison of findings in future studies that administer the MCCB. However, as is common in longitudinal studies, a proportion of the sample was lost to follow-up rendering a relatively low sample size which may have reduced statistical power to detect more subtle effects. Additionally, it is possible that the reduced performance in verbal learning and the two measures of processing speed over time may not be directly attributed to the presence of an initial psychotic episode. Other factors that typically co-occur with the onset of psychotic disorders such as social isolation, lack of employment or education may also impact adversely on neurodevelopment and these cognitive skills.

**CONCLUSION**

Widespread cognitive deficits persist over four years after an initial psychotic episode. There was a tendency for stable deficit in the majority of cognitive deficits, with the exception of verbal learning and two measures of processing speed, which have a marked poorer trajectory. However, these cognitive impairments in psychosis are malleable as cognitive remediation has improved performance in first episode psychosis and schizophrenia (Østergaard Christensen et al., 2014; Sartory et al., 2005). Speed of processing performance may moderate deficits in additional cognitive domains in psychosis and negative symptoms four years after a psychotic episode appeared to be partially predicted by performance on reasoning and problem solving and social cognition at illness onset. Targeted early cognitive remediation intervention therefore appears valuable and could potentially impact the course of negative symptoms following a first psychotic episode.
REFERENCES


THE ROLE OF THE ARCUATE FASCICULUS AND ASSOCIATED CORTICES IN VERBAL DEFICITS IN PSYCHOSIS

Joanne Kenney1*, Genevieve McPhilemy1, Cathy Scanlon1, Pablo Najt1, Shane McInerney1,2,3, Sophia Arndt1, Elisabeth Scherz1, Fintan Byrne1, Alexander Leemans4, Ben Jeurissen5, Brian Hallahan1, Colm McDonald1, Dara M. Cannon1

1 Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway, H91 TK33, Galway, Ireland
2 Department of Psychiatry, St Michaels Hospital, Toronto, Canada
3 Department of Psychiatry, University of Toronto, Canada
4 Images Sciences Institute, University Medical Centre Utrecht, The Netherlands
5 iMinds-Vision Lab, University of Antwerp, Belgium

Schizophrenia Bulletin, submitted
ABSTRACT

Background: Verbal learning (VL) and verbal fluency (VF) are prominent cognitive deficits in psychosis. The precise neuroanatomical contributions to these deficits are not fully understood. We aimed to investigate the arcuate fasciculus (AF) and its associated cortical regions to identify any structural abnormalities contributing to these verbal impairments in the early stage of psychotic illness.

Methods: Twenty-six individuals with recent onset psychosis and 27 healthy controls underwent cognitive testing using the MATRICS Consensus Cognitive Battery and structural and diffusion-weighted MRI. Bilaterally, anisotropy of the AF along with cortical thickness, surface area and volume of seven cortical regions were investigated in relation to VL and VF performance in both groups.

Results: Reduced surface area ($r=-0.61, p=0.003$) and volume ($r=-0.60, p=0.003$) of the right superior temporal gyrus was related to better VF in the controls. In the psychosis group higher volume of the right pars opercularis ($r=0.64, p=0.003$) and reduced lateralization of this cortical region ($r=-0.76, p=0.0002$) were positively associated with VL, while greater fractional anisotropy in the right long AF segment ($r=0.57, p=0.011$) and greater volume in the right pars orbitalis ($r=-0.62, p=0.004$) related to better VF, these findings were not present in controls. The psychosis group also had reduced right pars orbitalis thickness compared to controls ($F=10.25, p=0.003$).

Conclusion: The anatomical substrates for normal processing of VL and VF appear altered in recent onset psychosis. An aberrant role of the right hemisphere arcuate fasciculus and fronto-temporal cortical regions in individuals with psychosis may contribute to the deficits in VL and VF.
INTRODUCTION

Cognitive deficits are prevalent in early stages of psychosis, deficits of verbal cognition being the most consistent in the literature (Aas et al., 2014), which may also be susceptible to further deterioration longitudinally (Bozikas et al., 2011). In a previous study, we identified verbal learning and verbal fluency to remain persistently impaired compared to other cognitive domains four years subsequent to a first episode of psychosis (Kenney et al., 2015). These verbal deficits have been linked to functional outcome (Lin et al., 2011) and positive symptoms of the disorder (Lencz et al., 2006; Klosterkotter et al., 2016) and it is therefore vital to understand the precise neuroanatomical contributions of these cognitive impairments to assist in early diagnosis and targeted therapeutic interventions. In schizophrenia, structural and functional abnormalities have been found in language related brain regions such as the arcuate fasciculus (AF) (De Weijer et al., 2013). This white matter tract is strongly implicated in verbal abilities as lesions to the AF have been linked with disorders of language such as conduction aphasia (Wernicke et al., 1874). However, its involvement in verbal impairments in psychosis is not yet certain. The classical model of the (AF), as identified by gross dissection studies, is described as a long direct tract originating in the caudal temporal lobe including Wernicke’s territory, sweeping around the insula and sylvian fissure and connecting with the posterior portion of the inferior frontal lobule, synonymous with Broca’s regions. More recently, with the advent of modern diffusion tensor imaging (DTI) techniques, in vivo reconstruction of the arcuate fasciculus has revealed an additional two indirect tracts of the AF, the anterior tract linking the inferior-parietal lobule (Geschwind’s territory) to frontal regions and a posterior tract connecting Geschwind’s territory with temporal regions (Catani et al., 2005) (Figure 1). Most DTI studies investigating the AF use a measure of white matter microstructural organization called Fractional Anisotropy (FA), which is limited by its inconsideration of voxels which include crossing fibres (Dell’Acqua et al., 2013). This study will employ a novel measure called hindrance modulated orientational anisotropy (HMOA) to study the AF, which addresses this limitation.

Reduced FA has been found bilaterally in the arcuate fasciculus in schizophrenia compared to healthy controls (Shergill et al., 2007; Catani et al., 2011), although more consistently in the left tract exclusively, and has been associated with auditory verbal hallucinations (AVHs) (De Weijer et al., 2011). The cortical terminations of the arcuate fasciculus includes the inferior frontal gyrus, consisting of pars triangularis, pars orbitalis and pars opercularis; the inferior parietal cortex consisting of angular and supramarginal gyri; and the superior,
middle and inferior temporal gyri (Francis et al., 2012). Greater cortical thickness in frontal, temporal and parietal language regions have been linked to better verbal abilities in healthy adults (Hartberg et al., 2010; Antonova et al., 2005). While reduced thickness and functional activation in these areas have been found in schizophrenia (Ehrlich et al., 2012; Jeong et al., 2009; Vita et al., 1995), evidence of cortical abnormalities has not been attributed directly to verbal deficits in psychosis. However, verbal scores have been found to be associated with regions in the right hemisphere such as the inferior frontal gyrus and superior temporal gyrus in schizophrenia (Ehrlich et al., 2012). Therefore, this study aims to investigate if structural abnormalities are present in the AF and its associated cortical regions and the contribution these abnormalities make to the deficits in verbal cognitive performance in psychosis.

A secondary goal of the study is to examine asymmetry patterns of the AF network. The left hemisphere shows a prominence for language function (Ehrlich et al., 2012; Bethmann et al., 2007). The long segment of the AF demonstrates a leftward asymmetry in healthy individuals (Catani et al., 2007; Vernooij et al., 2007) and plays a dominant functional role in language (Vassal et al., 2016). The anterior AF tract has been found to predominantly present a rightward symmetry and a bilateral distribution is evident in the posterior segment (Catani et al., 2007). Abnormalities in the asymmetry of the AF are suggested to occur in schizophrenia which may contribute to positive symptoms of the disorder (Abdul-Rahman et al., 2012) although findings are heterogeneous with some studies finding no abnormal laterality patterns (25). Cortical asymmetries in the human brain are more subtle (Crow et al., 2004). The most consistently reported left lateralized structure, the planum temporale (PT), (Shapleske et al., 2001; Harasty et al., 2003), is implicated in language function and synonymous with a portion of Wernicke’s region. Despite heterogeneous findings due to methodological inconsistencies, the PT appears to have reduced leftward asymmetry in schizophrenia (Shapleske et al., 1999; Hasan et al., 2011) and has been associated with clinical symptoms (Oertel-Knochel et al., 2011). Reduced left laterality has also been reported in the volume of the STG in schizophrenia and linked with cognitive deficits (Vita et al., 1995). Therefore we aim to examine if reductions in normal asymmetry of the AF and the language related cortical structures to which this tract projects to contribute to verbal learning and verbal fluency deficits in psychosis. The majority of imaging studies investigating brain laterality employ measures of cortical surface area and cortical volume (Shapleske et al., 1999). As cortical volume (CV) alone is not an optimal measure of asymmetry due it being a product of two independent measures, cortical thickness (CT) and
surface area (CSA) (Meyer et al., 2014), this study will combine these three indices of cortical measurement in its analysis (CT, CSA, CV) and to our knowledge is the first study to do so in examining laterality patterns in schizophrenia.

Finally, FA of the AF has been positively associated with cortical thickness in regions such as superior and middle temporal gyrus, supramarginal gyrus and inferior frontal gyrus in healthy controls, more pronounced in the left hemisphere (Phillips et al., 2011). Therefore, we aim to extend this investigation in controls using HMOA, and also investigating the relationship in individuals with psychosis.

In summary, using structural and diffusion MRI, the current study aims to investigate microstructural organization of three segments of the arcuate fasciculus and the cortical thickness, volume and surface area of seven of its cortical terminations, to determine whether abnormalities in the structures or in the laterality patterns of these brain regions contribute to impairments in verbal learning and verbal fluency in psychosis. As many brain abnormalities in schizophrenia are small and subtle in nature (Shenton et al., 2001), segregated points along each AF segment will be additionally examined in relation to verbal cognition. Uncovering neuroanatomical determinants of these verbal deficits could further our understanding of cognitive impairments of the disorder.

The main objectives and hypotheses are summarised below:

**Objective 1**

To investigate whether differences exist between individuals with psychosis and healthy controls in the neuroanatomy of the AF and cortical regions.

**Hypothesis 1**

Individuals with psychosis will have reduced HMOA/FA in the AF and reduced cortical thickness in frontal, temporal lobes and the inferior parietal lobe bilaterally compared to healthy controls, particularly in the left hemisphere.

**Objective 2**

To investigate the relationship between the AF and cortical regions in relation to verbal learning and verbal fluency in both healthy controls and individuals with psychosis.
**Hypothesis 2**

In healthy controls, verbal learning/fluency will be positively associated with HMOA/FA of the AF, specifically in the left hemisphere. Verbal learning/fluency will also be positively associated with cortical thickness of cortical regions (frontal/temporal/parietal regions).

Despite a lack of evidence in the current literature leading to a directional hypothesis regarding the individuals with psychosis, we aim to explore the relationship between verbal learning/fluency and HMOA/FA of the AF. In this group, it is hypothesised that verbal scores will be positively associated with the regional surface area and volume in the right hemisphere such as the inferior frontal gyrus and superior temporal gyrus.

**Objective 3**

To investigate the patterns of laterality of the AF and the cortical regions in both individuals with psychosis and healthy controls and also to assess the relationship between laterality and verbal cognition in both groups.

**Hypothesis 3**

Individuals with psychosis will have a reduction of the normal left laterality evident in healthy controls, particularly in the superior temporal gyrus which encompasses the planum temporale. In individuals with psychosis, there will be a negative association (or a reduced left laterality) between the laterality index in cortical regions such as the superior temporal gyrus and verbal scores.

**Objective 4**

To investigate the relationship between microstructural organisation of the AF and the cortical regions where it is known to project to.

**Hypothesis 4**

In healthy controls, there will be a positive association between HMOA/FA of the AF and cortical thickness in regions such as superior and middle temporal gyrus, supramarginal gyrus and inferior frontal gyrus, more pronounced in the left hemisphere.
We aim to conduct exploratory analysis investigating the relationship between HMOA/FA of the AF and cortical regions in both hemispheres.
Figure 1. (A) The three segments of the AF and (B) the combined three segments of the arcuate fasciculus. (C) Seven cortical regions where the arcuate fasciculus is known to project to.
METHODS AND MATERIALS

Participants

Twenty-six individuals with recent onset of psychotic illness and 27 healthy controls (HC), participated in the study (Table 1). Participants underwent cognitive testing and MR scanning at first-presentation of illness and four years later (follow-up), the latter time-point, which included a diffusion tensor imaging acquisition, was used in the current analysis. All subjects were aged between 19 and 59 years. The recruitment and clinical assessment of these individuals are described previously (Scanlon et al., 2014; McFarland et al., 2013). Exclusion criteria for all participants included neurological disorders (including epilepsy), comorbid substance or alcohol abuse in the last year, a history of head injury resulting in loss of consciousness for over 5 min, oral steroid use in the previous 3 months and general contraindications to MRI. Healthy controls were also excluded if they had a personal or family history of psychotic or affective disorder. The study was approved by the research Ethics Committees of the National University of Ireland Galway and Galway University Hospitals. Written informed consent was obtained from all participants.
Table 1. Demographic characteristics and clinical features of the study sample

<table>
<thead>
<tr>
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<th>Individuals with psychosis</th>
<th>Healthy controls</th>
<th>Statistics (t/χ², p)</th>
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</thead>
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<tr>
<td><strong>N</strong></td>
<td>26</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age (Mean yrs±SD)</td>
<td>32±9</td>
<td>38±9</td>
<td>2.43, 0.02*</td>
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<tr>
<td>Gender N (m,f) (%)fem</td>
<td>16,10 (31%)</td>
<td>15,12 (20%)</td>
<td>0.20, 0.70</td>
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<tr>
<td>Education (Mean yrs±SD)</td>
<td>16.1±2.8</td>
<td>17.3±3.4</td>
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<td>Handedness (left/right)</td>
<td>4/22</td>
<td>2/25</td>
<td>8.4, 0.36</td>
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<td><strong>Diagnosis (N)</strong></td>
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<tr>
<td>Schizophrenia</td>
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<td>Psychosis NOS</td>
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<tr>
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<tr>
<td>CPZ equivalents @ FU</td>
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<tr>
<td>CPZ equivalents total</td>
<td>245421±260750</td>
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<tr>
<td><strong>Symptoms: PANSS</strong></td>
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<tr>
<td>Total score</td>
<td>43.73±14.4</td>
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<tr>
<td>Positive score</td>
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<td>Negative score</td>
<td>11.2±6.4</td>
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<tr>
<td>General score</td>
<td>22.6±6.3</td>
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</table>

**Legend:** SD = standard deviation, † = antipsychotic medication was converted to chlorpromazine equivalents (Lehman et al., 1998; Taylor et al., 2007; Woods, 2003); * = significant difference between groups in age, N = number, PANSS = positive and negative symptom scale (0-6 per item scale version), FU = follow-up.
**Cognitive Measures**

The MATRICS Consensus Cognitive Battery (MCCB) was administered to individuals with psychosis and to a healthy control group. The MCCB assesses 7 cognitive domains known to be impaired in schizophrenia (Kern et al., 2008). Two cognitive tests from the battery, verbal learning (Hopkins Verbal Learning Test –Revised) and verbal fluency (Category fluency: Animal fluency) were used in the current analyses (see (3) for description of cognitive tests).

**MRI Acquisition**

All subjects underwent structural MR and diffusion imaging at University Hospital Galway (UHG) in a 1.5 Tesla Siemens Magnetom Symphony scanner (Erlangen, Germany) equipped with a 4-channel head coil. A volumetric T1-weighted magnetization-prepared rapid acquisition of gradient echo (MPRAGE) sequence was acquired with the imaging parameters: Repetition time (TR): 1140ms, echo time (TE): 4.38ms, inversion Time (TI): 600ms, flip angle 15°; matrix size 256x256; an in-plane pixel size of 0.9mmx0.9mm and slice thickness of 0.9mm. Whole brain high angular resolution data was obtained in the axial orientation along 64 independent diffusion gradient directions, b-value = 1300 s/mm², with 7 reference non-diffusion-weighted images (b-value = 0 s/mm²). Image parameters were: echo time (TE) = 95 ms, repetition time (TR) = 8100 ms, flip angle = 15°, voxel size = 2.5 mm³, matrix size= 96 x 96, slice thickness = 2.5 mm, in-plane resolution = 2.5 mm².

**Image processing and Quality Assessment – Diffusion Data**

Explore DTI (version 4.8.4) was used to correct for motion and eddy current induced geometric distortions including rotation of the b-matrix to preserve the orientation information (Leemans et al., 2009a; Leemans et al., 2009b). Data quality was further assessed by visual inspection (Tournier et al., 2011). Whole brain tractography was carried out in ExploreDTI using the constrained spherical deconvolution (CSD) tracking algorithm (Jeurissen et al., 2011) with recursive calibration of the response function (Tax et al., 2013). The three segments of the AF, long, anterior and posterior, were isolated based on a strict anatomical protocol (Catani et al., 2007) by manually placing AND and NOT gates on directionally encoded colour anisotropy (DEC-FA) maps (See Supplementary material 1 for protocol description). Median HMOA and median FA of the bilateral three AF segments were extracted. Tract volume was covaried for when analyzing the FA of the segments. Additional tract resampling of the three segments was performed at a number of points over the length
of each tract (mean length of tract divided by voxel size). The long tract was subdivided into 32 sections, the anterior tract into 23 sections and the posterior tract into 14 sections. Median HMOA and median FA were extracted at each section (Figure 2).

**Figure 2.** The long tract of the arcuate fasciculus was resampled at 32 points along the tract and the fibre bundle reduced to a single averaged tract. ANCOVAs were conducted at each of the 32 points of the reduced average tract, to determine group differences at each point.

Uniform resampling of long tract of arcuate Fasciculus to 32 points

Fibre bundle reduced to single averaged tract

**Image Processing and Quality Assessment—Structural Data**

Intensity inhomogeneities in the T1-weighted images were corrected using nonparametric, non-uniform intensity normalization (N3) (Sled et al., 1998). Image processing was carried out using FreeSurfer, stable version 5.1 (https://surfer.nmr.mgh.harvard.edu). Detailed descriptions of this method have already been reported (Scanlon et al., 2014; Dale et al., 1999; Fischl et al., 1999), but are briefly summarized in Supplementary material 2.

**Statistics**

All statistics were conducted using IBM SPSS (v.21) (IBM Corp, 2012). ANCOVAs were used to identify any group differences in the three tracts of the arcuate fasciculus (median HMOA of the segment and at each point along each segment) and in the cortical thickness (CT), surface area (CSA) and volume (CV) of cortical regions bilaterally. Kruskal-Wallis tests were administered for any points along each AF segment that were not normally distributed. Partial correlation analyses were implemented for the psychosis group and the healthy controls when investigating the relationship between the AF and cortical regions with verbal
learning and verbal fluency, and additionally when examining the association between AF anisotropy and cortical regions.

For each AF segment and cortical region (CT, CSA, CV) a lateralization index (LI) was calculated according to the formula (e.g. for HMOA: left HMOA-right HMOA/ left HMOA+right HMOA). A positive value indicated a leftward asymmetry and a negative indicated a rightward asymmetry. The degree of lateralization was determined using a one-sample t-test. ANCOVA models were implemented when investigating group differences in LI. For non-normally distributed LIs, non-parametric Mann-Whitney tests were conducted.

To correct for multiple comparisons, false discovery rate (FDR) correction was applied for all analyses. Left-handed individuals were removed (n=6; Table 1), with age and gender being covaried for all analyses. Shapiro–Wilks tests were used to test for normal distribution of each variable investigated. The majority of variables were normally distributed with any non-normal distributions successfully transformed (See Supplementary material 3). As the most novel measure of white matter organization, HMOA, is not a well-established measure of microstructural organisation in the literature, it is presented along a conventional index, FA, in this paper. FA of the arcuate fasciculus was investigated post-hoc and results are included in Supplementary Material 4.
**RESULTS**

**Group differences in verbal learning and verbal fluency**

The individuals with psychosis had significantly reduced verbal learning (VL) and verbal fluency (VF) scores compared to healthy controls (Figure 3A).

**Figure 3.** (A) Individuals with psychosis performed significantly poorer on verbal learning and verbal fluency compared to healthy controls (HC); (B) Individuals with psychosis had lower cortical thickness compared to healthy controls (HC) in the right hemisphere pars orbitalis which is part of the inferior frontal gyrus.

![Graph showing verbal learning and verbal fluency](image1.png)

![Graph showing cortical thickness](image2.png)
Group Differences in the Arcuate Fasciculus and Relationship to Verbal Cognition

HMOA: There were no significant differences between the individuals with psychosis and controls in the median HMOA of the long, anterior or posterior segments (F=0.01-3.59, p=0.10-0.91), nor at any individual points investigated along the three AF segments with FDR correction (uncorrected significance levels are shown in Figure 4), not in support of hypothesis 1. Additionally, hypothesis 2 was not supported when using HMOA, as none of the AF segments did not relate significantly to verbal learning (r=-0.16-0.24, p=0.16-0.66) or verbal fluency (r=-0.14-0.28, p=0.09-0.73) in either group, nor was there any significant relationships between these measures and HMOA at any location along the segments (VL: r=-0.1-0.35, p=0.03-0.86; VF: r=-0.18-0.24, p= 0.13-0.84).

FA: When investigating group differences of the FA of the arcuate fasciculus, the magnitude and direction of results were similar to HMOA findings (Supplementary 4A). However, in contrast to HMOA results, a significant correlation between the right long segment and verbal fluency was evident in the psychosis group (Supplementary 4B).

Figure 4. Sections along each of the three segments of the AF that had significant group differences (uncorrected p values)
Group Differences in Associated Cortices of the Arcuate Fasciculus and Relationship to Verbal Cognition

In support of hypothesis 1, in the right hemisphere, the individuals with psychosis had significantly reduced cortical thickness in the pars orbitalis (mean±SE:2.63±0.04) compared to controls (mean±SE:2.83±0.04), (F=10.25, p=0.003) (Figure 3B). There were no further significant group differences surviving multiple comparisons correction in the thickness, surface area or volume of any cortical regions (F=0.03-6.68, p=0.013-0.87).

Lower surface area (r=-0.61, p=0.003) and volume (r=-0.60, p=0.003) of the right superior temporal gyrus (STG) was significantly associated with greater verbal fluency performance in the control group (Figure 5A,B). This finding partially supported hypothesis 2 due to the association between verbal scores and cortical regions, although associations in controls were in the opposite direction to what was hypothesised, and in the right hemisphere only and not the left as hypothesised. In the psychosis group, greater volume in the right pars orbitalis was significantly associated with greater verbal fluency (r=0.62, p=0.004) (Figure 5C), while greater volume in the right pars opercularis was significantly related to better verbal learning scores (r=0.64, p=0.003) (Figure 5D), in support of hypothesis 2. No other significant correlations were found between the thickness, surface area and volume of any other cortical regions and verbal learning (r=-0.23-0.36, p=0.02-0.98) or verbal fluency (r=-0.46-0.22, p=0.02-0.99).
Figure 5: Reduced surface area (A) and volume (B) in the right STG was correlated with better performance on a verbal fluency task (log transformed) in healthy controls. For the individuals with psychosis, better verbal fluency performance was related to greater volume in the right pars orbitalis (C) while greater volume in the right pars opercularis (D) and reduced left lateralization (volume) of the pars opercularis (E) was associated with better verbal learning performance.
Patterns of Lateralization of the Arcuate Fasciculus and Relationship to Verbal Cognition

**HMOA:** In the healthy controls, the lateralization index (LI-HMOA) of the long and posterior segment displayed significant leftward asymmetry patterns, while the anterior segment was significantly rightward in its symmetry (Figure 6). In the individuals with psychosis, a leftward asymmetry was present in the long segment, with no significant asymmetry patterns evident in the anterior or posterior segments (Figure 6). Individuals with psychosis and healthy controls did not significantly differ in the laterality patterns of the three AF segments (F=0.42-3.37, p=0.08-0.52). When investigating the relationship with cognition, there were no significant associations between the asymmetry of the three AF segments and verbal learning or verbal fluency (Figure 6).

**FA:** When investigating laterality with measures of FA (LI-FA), the magnitude and direction of results were similar to HMOA, with the exception of no significant asymmetry reported in the posterior segment of the healthy controls. Similar to HMOA, no group differences in laterality were reported and laterality did not significantly relate to cognition (Supplementary 4C).
Figure 6. Laterality patterns of the long, anterior and posterior segments of the arcuate fasciculus in healthy controls (HC) and individuals with psychosis.

Legend: * = significant laterality patterns in the arcuate fasciculus; HC = healthy control; LI = lateralization index; ** = relationship of LI to verbal learning and verbal fluency, covarying for age and gender.
Patterns of Lateralization of the Associated Cortices of the Arcuate Fasciculus and Relationship to Verbal Cognition

Investigating laterality patterns of cortical thickness revealed a significant leftward asymmetry in the inferior temporal gyrus of the healthy controls. Individuals with psychosis demonstrated no significant asymmetry patterns in the thickness of any cortical regions (Supplementary 5). Investigating cortical surface area (CSA) revealed a significant leftward asymmetry in the pars opercularis, STG and ITG, and a significant rightward asymmetry in the pars triangularis, pars orbitalis and MTG. Individuals with psychosis demonstrated similar directions of cortical symmetry to controls with the exception of no significant STG asymmetry. CV laterality revealed identical symmetry patterns to CSA in controls and similar symmetry patterns to CSA in individuals with psychosis excepting differences in the STG and ITG (Supplementary 5).

Not in support of hypothesis 3, individuals with psychosis and controls did not significantly differ in the LI of any cortical regions (thickness, surface area or volume) (Supplementary 6). However, partially supporting hypothesis 3 when investigating the relationship with cognition, we found a relationship between reduced left lateralization of the volume of the pars opercularis and better verbal learning ($r=0.76, p=0.0002$) (Figure 5E) in the psychosis group, although not in present in the STG as hypothesised. There were no other significant relationships between laterality and cognition in both groups (VL: $r=0.59-0.41, p=0.008-0.89$; VF: $r=0.44-0.47, p=0.04-96$).

Relationship between the Arcuate Fasciculus and Its Associated Cortices

**HMOA:** There were no significant relationships between any of the three AF segments and cortical regions (thickness, surface area or volume) in either group ($r=0.29-0.50, p=0.03-0.98$).

**FA:** When investigating measures of FA, significant associations were identified in the control group between the left anterior segment and the left pars orbitalis thickness ($r=-0.60, p=0.003$) and the left supramarginal gyrus thickness ($r=-0.59, p=0.004$) in support of hypothesis 4. No other significant associations were found in either group ($r=-0.43-0.59, p=0.008-0.98$).
DISCUSSION

The current study, which included a comprehensive investigation of the arcuate fasciculus (AF) language network in relation to verbal cognitive deficits in psychosis, identified predominant findings in the right hemisphere neuroanatomy of this network which may contribute to these cognitive impairments. Microstructural organisation of the right long segment of the AF as indexed by FA was related to verbal fluency performance in individuals with psychosis. This relationship was not evident in healthy controls and may be indicative of a pathological role of this tract in verbal fluency performance. Previously, the right AF has been identified as a potential trait marker for schizophrenia and has shown trends of a relationship with positive symptoms (Wu et al., 2014). The magnitude and direction of results for HMOA of the right long AF was consistent with FA, though not statistically significant. In relation to cortical regions, the psychosis group revealed a positive association between cortical volume in the right pars opercularis and pars orbitalis and better performance in VL and VF respectively. Additionally, reduced left asymmetry in the volume of the pars opercularis was associated with better VL in psychosis. Combined, our findings may implicate an abnormal involvement of right inferior frontal gyri cortical regions in verbal tasks in psychosis, as in healthy individuals this region plays a limited role in language lacking any phonological or semantic representation, with the right pars opercularis specifically activated by tonal and pseudowords (Vigneau et al., 2011). Additionally, we found reduced thickness in the right pars orbitalis in the psychosis group, which has previously been reported in early stages of the illness (Francis et al., 2012).

In healthy controls, a reduction in the right hemisphere superior temporal gyrus (STG) volume and surface area was associated with greater verbal fluency performance, not present in the psychosis group. PET and fMRI studies show that verbal fluency tasks activate frontal regions coupled with a deactivation in bilateral STG (Schlosser et al., 1998; Frith et al., 1995) with a failure of STG deactivation suggested to occur in schizophrenia (Frith et al., 1995; Fletcher et al., 1996). The absence of reduced STG volume involvement in verbal fluency performance in the psychosis group may indicate pathology in this cortical region contributing to impairments on this task. However, it is uncertain precisely how functional activation of the STG relates to volume of the cortex. An alternative interpretation may be that normal synaptic pruning in the STG which results in greater vocabulary specialization (Sowell et al., 2004) may correspondingly not occur in individuals with psychosis. One previous study reported increased performance in verbal fluency to be associated with
decreased thickness in bilateral STG, among other language regions (Porter et al., 2011).

Distinct patterns of laterality in the three segments of the AF were evident. In healthy controls, we found a left asymmetry in the long and posterior segment, whereas the anterior segment was rightward lateralized, consistent with previous research excepting the posterior segment which was previously reported to be bilateral (Catani et al., 2007). A leftward asymmetry was found in the long segment in the psychosis group. Analyses of cortical surface area and cortical volume revealed similar patterns of asymmetry in multiple regions consistent with previous studies (Meyer et al., 2014). Analysis of cortical thickness revealed a significant leftward pattern in the inferior temporal gyrus in controls only. The current study did not find any abnormal laterality patterns in the psychosis group in the arcuate fasciculus or associated cortical regions. Previous studies indicate slight attenuation in the normal lateralization pattern in schizophrenia (Park et al., 2004), however studies regarding the arcuate fasciculus and cortical asymmetry are heterogeneous, with some studies showing no differences between patients and controls (Miyata et al., 2012; Hamilton et al., 2007; Takao et al., 2010; Meisenzahl et al., 2004). While the planum temporale (PT) is the most consistently reported region exhibiting abnormal asymmetry in schizophrenia, this study did not investigate the PT explicitly but rather the entire STG region which may have obscured any true abnormal asymmetry in the PT.

Contrasting to other studies where abnormal increases or decreases in FA of the AF have been found in psychosis (Rotarska-Jagiela et al., 2009; Shergill et al., 2007), this study failed to find any abnormalities in HMOA or FA of the AF in individuals with psychosis relative to controls. Variability of findings may be due to differences in the anatomical definitions of the AF employed in studies and the fact that the body of the three AF segments were examined only, excluding tract endings to reduce variance. The current study did not report any relationship between HMOA of the three AF segments and its associated cortical regions in contrast to other studies using FA (Phillips et al., 2011). However, post-hoc analysis of FA measures did find a relationship between the left AF and left frontal and parietal cortical regions in the control group.

The importance of investigating language related brain regions and verbal deficits in schizophrenia is highlighted by the relationship between verbal cognition and auditory verbal hallucinations (AVHs) (Gisselgard et al., 2014) which may share similar neural substrates. Deficits in verbal cognitive tasks and abnormalities in the brain networks involved may be
potential markers of development of auditory verbal hallucinations (AVH) (Lencz et al., 2006; Klosterkotter et al., 2016). Our findings mainly suggest a dysfunctional role of the right hemisphere, in the right long AF segment and right frontal and temporal cortices which this AF segment projects to. AVHs have been associated with activation of the right inferior frontal area (Sommer et al., 2008), and to impaired connectivity in fronto-temporal language regions (Curcic-Blake et al., 2013), therefore our findings could potentially support the involvement of fronto-temporal cortical abnormalities in language function and potentially psychotic symptoms in psychosis. Post-hoc analysis revealed that our finding of an association between asymmetry of the pars opercularis and verbal learning in the psychosis group was driven by those experiencing AVHs (Supplementary 7). Sample size and consequently statistical power was low, therefore it is recommended that future studies explicitly investigate the role of abnormal cortical asymmetry in auditory verbal hallucinations.

Strengths of the current study include a comprehensive exploration of the AF using a novel measure of anisotropy (HMOA) and a detailed examination of the language cortical regions using three indices of grey matter architecture, in relation to verbal deficits in psychosis. Limitations of the study include the limited sample size and clinical heterogeneity of the sample. As the response function of the HMOA, which represents the diffusion signal profile of white matter fibre orientation, is individually optimised, it is unclear what effect non-normalisation of the response function has on findings in the current study and future investigation into this is warranted. Also, the correlational nature of the analysis renders it possible only to infer associations between the language network studied and verbal cognitive measures.

CONCLUSION

In summary, our findings suggest a dysfunctional role of the right hemisphere long arcuate fasciculus segment and right frontal and temporal cortices in verbal learning and verbal fluency impairments in psychosis. Abnormal laterality in the pars opercularis may also contribute to verbal learning deficits in psychosis, thereby further implicating an atypical role of the right inferior frontal gyrus in verbal cognitive tasks in psychotic illness.
REFERENCES


SUPPLEMENTARY MATERIAL

S1. Protocol for delineation of the three segments of the arcuate fasciculus

The long tract of the arcuate fasciculus was isolated with a frontal AND gate in the coronal plane 1mm anterior to the upper boundary of the corpus callosum and around the periventricular anterior/posterior running fibres located lateral to the projection fibres of the corona radiata. A second, temporal AND gate was placed in the axial plane, lateral to the posterior horn of the lateral ventricle, 4mm posterior to the last slice where the fibre curves around the posterior and medial extent of the Sylvian fissure, the AND gate extending around the majority of the temporal lobe (Figure S1A). The anterior tract was isolated using the frontal gate implemented for the long segment and a parietal AND gate placed on the sagittal plane, 3mm lateral to the emergence of the fibres arching around the Sylvian fissure to include the region medial to the supramarginal gyrus, (Figure S1B). The posterior tract was isolated using the parietal and temporal gates (Figure S1C). The posterior tract was isolated using the parietal and temporal gates (Figure S1C). NOT gates were applied to remove any spurious tracts and tract areas external to the defined gates were excluded to include the main body of each tract in analysis. Both left and right segments were isolated with this protocol.
Figure S1: (A) Frontal and temporal AND gates placed on DEC-FA map to isolate the long tract of the arcuate fasciculus (AF); (B) the frontal gate in addition to the parietal gate were used to extract the anterior tract; (C) the parietal gate was used in conjunction with the temporal gate to isolate the posterior tract of the AF.
S2. FreeSurfer Processing – Cortical analysis

Based on a linear combination of voxel intensities and local geometric constraints, the cerebral white matter (WM) is first segmented, divided into 2 hemispheres, and the brain stem and cerebellum removed. Tessellation is then performed to produce a triangle-based mesh of the WM surface and refined to alleviate the voxel-based nature of the initial curvature. The WM surfaces are deformed outward to generate the pial (GM/CSF intersection) surface. Topologic defects in the surface are corrected using an automated topology fixer. Visual quality checks were then performed and inaccuracies manually edited and corrected by reprocessing. The cortical surface is then spherically inflated so that the entire cortical surface is exposed, including deep tissue inside the sulci. Using combined information from the pial and WM surfaces, cortical thickness, surface area and volume are calculated at each vertex. Seven language-related bilateral cortical regions, where the arcuate fasciculus is known to project to, were isolated from each individual cortex using an automated parcellation process based on the Desikan-Killany cortical atlas (Desikan et al., 2006) implemented in FreeSurfer (Figure 1). The pars opercularis, pars triangularis and pars orbitalis were chosen as the rostral cortical regions where frontal projections of the long and anterior AF segment terminate. Temporal terminations of the long and posterior segment were identified as the superior, middle and inferior temporal gyri (Rilling et al., 2008, Dick & Tremblay, 2012). The supramarginal gyrus was identified as the posterior termination of the anterior segment and the superior lateral termination of the posterior segment.
**S3. Results of normal distribution testing using Shapiro–Wilk**

**Cognition:** Verbal learning was normally distributed \((w=0.97, p=0.45)\). Verbal fluency was non-normal \((w=0.93, p=0.005)\), however became normally distributed following log transformation \((w=0.96, p=0.10)\).

**Arcuate fasciculus:** Left and right AF segments were all normally distributed \((w=0.95-0.99, p=0.06-0.99)\).

**Cortex:** The cortical thickness of the right hemisphere pars opercularis was non-normally distributed \((w=0.94, p=0.02)\) but became so after log transformation \((w=0.96, p=0.16)\). All other cortical regions were normally distributed \((w=0.94-0.99, p=0.07-0.95)\). The cortical surface area of the right hemisphere pars triangularis \((w=0.92, p=0.004)\) and ITG \((w=0.94, p=0.02)\) were non-normal both becoming significant following log transformation for the pars triangularis \((w=0.96, p=0.16)\) and square transformation for the ITG \((w=0.96, p=0.1)\). All other regions were normally distributed for surface area \((w=0.92-0.99, p=0.07-0.96)\) and cortical volume \((w=0.96-0.99, p=0.07-0.90)\).

**Lateralization index:** The lateralization index of all three AF segments were normally distributed \((w=0.97-0.98; p=0.18-0.61)\). All lateralization indices (LI) of cortical thickness were normally distributed \((w=0.93-0.98; p=0.19-0.87)\) excepting the LI of the pars triangularis \((w=0.92, p=0.005)\), MTG \((w=0.94, p=0.02)\) and ITG \((w=0.94, p=0.014)\). All LIs of the cortex using surface area measures were normally distributed \((w=0.96-0.99, p=0.19-0.98)\) with the exception of the STG \((w=0.77, p=0.00)\). Using cortical volume, the LI of all cortical regions were normally distributed \((w=0.96-0.99, p=0.19-0.98)\) except for the STG \((w=0.85, p=0.00)\) and the exception of the STG \((w=0.85, p=0.00)\). Non-parametric tests were used when analyzing the non-normally distributed LI variables as it was not possible to successfully transform these data.
S4. Results of investigations of the Fractional Anisotropy of the Arcuate Fasciculus

(A)

There were no significant differences between the individuals with psychosis and healthy controls in the FA of the long, anterior or posterior segments (F=0.001-1.15, p=0.29-0.77), nor at any individuals points investigated along the three AF segments which survived FDR correction.

(B)

Relationship to Verbal Cognition: In the individuals with psychosis, greater FA in the right long segment was positively associated with log transformed verbal fluency (r=0.57, p=0.011). There were no significant associations between FA of the bilateral long, anterior or posterior AF segments and verbal learning (r=-0.34-0.12, p=0.14-0.81) or verbal fluency (r=-0.28-0.36, p=0.14-0.72) in either group. There were no associations between points along each segment and verbal learning (r=-0.64-0.54, p=0.003-0.89) or verbal fluency (r=-0.22-0.26, p=-0.22-0.92), following FDR correction.
### Patterns of lateralization (FA)

<table>
<thead>
<tr>
<th>Healthy Controls</th>
<th>Difference from 0</th>
<th>Direction</th>
<th>VL**</th>
<th>VF**</th>
</tr>
</thead>
<tbody>
<tr>
<td>LI Long</td>
<td>3.84,0.01*</td>
<td>0.078</td>
<td>Left</td>
<td>-0.04,0.85</td>
</tr>
<tr>
<td>LI Anterior</td>
<td>-3.86,0.001*</td>
<td>-0.071</td>
<td>Right</td>
<td>-0.12,0.59</td>
</tr>
<tr>
<td>LI Posterior</td>
<td>0.85,0.42</td>
<td>0.044</td>
<td>Left</td>
<td>0.29,0.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychosis</th>
<th>Difference from 0</th>
<th>Direction</th>
<th>VL**</th>
<th>VF**</th>
</tr>
</thead>
<tbody>
<tr>
<td>LI Long</td>
<td>3.2, 0.004*</td>
<td>0.04</td>
<td>Left</td>
<td>-0.34,0.17</td>
</tr>
<tr>
<td>LI Anterior</td>
<td>-2.27,0.03</td>
<td>-0.018</td>
<td>Right</td>
<td>-0.01,0.96</td>
</tr>
<tr>
<td>LI Posterior</td>
<td>0.73,0.47</td>
<td>0.043</td>
<td>Left</td>
<td>-0.31,0.21</td>
</tr>
</tbody>
</table>

**Legend:** LI = lateralisation index; * = significantly different from zero and survived FDR correction; ** = relationship of LI to verbal learning and verbal fluency, covarying for age and gender.

**Group Differences in Lateralization Patterns (FA):** A univariate ANOVA revealed that there was no significant differences between individuals with psychosis and healthy controls in the lateralisation index of the long (F=0.06,p=0.81), anterior (F=0.61,p=0.44) or posterior tract (F=0.68,p=0.42).
S5. Lateralization index (using measures of cortical thickness, surface area and volume) of seven language related cortical regions in healthy controls (A) and individuals with psychosis (B).

### A

<table>
<thead>
<tr>
<th>Cortical Region</th>
<th>T</th>
<th>p</th>
<th>Mean Diff</th>
<th>T</th>
<th>p</th>
<th>Mean Diff</th>
<th>T</th>
<th>p</th>
<th>Mean Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pars opercularis</td>
<td>-1.56,0.13</td>
<td>-0.011</td>
<td>4.11, 0.0004*</td>
<td>0.79</td>
<td>4.42,0.0001*</td>
<td>0.074</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Pars triangularis</td>
<td>1.55,0.14</td>
<td>0.007</td>
<td>-4.77,0.7e-5*</td>
<td>-0.064</td>
<td>-4.34,0.0002*</td>
<td>-0.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pars orbitalis</td>
<td>-0.53,0.60</td>
<td>-0.004</td>
<td>-9.11,0.0e-5*</td>
<td>-0.114</td>
<td>-6.91,0.0e-5*</td>
<td>-0.11</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>STG</td>
<td>0.56,0.58</td>
<td>0.003</td>
<td>2.54,0.018*</td>
<td>0.017</td>
<td>2.68,0.013*</td>
<td>0.017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTG</td>
<td>-0.22,0.83</td>
<td>-0.001</td>
<td>-3.93,0.001*</td>
<td>-0.035</td>
<td>-3.91,0.001*</td>
<td>-0.044</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITG</td>
<td>3.93,0.001*</td>
<td>0.013*</td>
<td>5.07,0.00004*</td>
<td>0.044</td>
<td>5.25,0.00002*</td>
<td>0.051</td>
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</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>0.009,0.99</td>
<td>0.0001</td>
<td>1.40,0.17</td>
<td>0.017</td>
<td>1.93,0.07</td>
<td>0.022</td>
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</tbody>
</table>

**Legend:** Note: Mean diff = mean difference from 0 - positive values indicate a leftward asymmetry, negative values indicate a rightward asymmetry; * = significantly different from zero.
**Legend:** Note: Mean diff = mean difference from 0 - positive values indicate a leftward asymmetry, negative values indicate a rightward asymmetry; * = significantly different from zero; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus.

<table>
<thead>
<tr>
<th>Region</th>
<th>t</th>
<th>p</th>
<th>Mean Diff</th>
<th>t</th>
<th>p</th>
<th>Mean Diff</th>
<th>t</th>
<th>p</th>
<th>Mean Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pars opercularis</td>
<td>-0.48,0.64</td>
<td>-0.004</td>
<td></td>
<td>6.30,0.3e-6*</td>
<td>0.113</td>
<td></td>
<td>6.70,0.01e-6*</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>Pars triangularis</td>
<td>-1.26,0.22</td>
<td>-0.009</td>
<td></td>
<td>-4.6,0.00015*</td>
<td>-0.071</td>
<td></td>
<td>-4.13,0.0005*</td>
<td>-0.084</td>
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</tr>
<tr>
<td>Pars orbitalis</td>
<td>0.70,0.49</td>
<td>0.006</td>
<td>-8.87,0.0e-6*</td>
<td>-0.122</td>
<td></td>
<td>-7.69,0.0e-6*</td>
<td>-0.101</td>
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<tr>
<td>STG</td>
<td>0.48,0.64</td>
<td>0.003</td>
<td>1.53,0.14</td>
<td>0.025</td>
<td></td>
<td>2.63,0.016*</td>
<td>0.044</td>
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<tr>
<td>MTG</td>
<td>0.59,0.56</td>
<td>0.003</td>
<td>-6.32,0.3e-5*</td>
<td>-0.066</td>
<td></td>
<td>-5.01,0.00006*</td>
<td>-0.07</td>
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</tr>
<tr>
<td>ITG</td>
<td>0.66,0.52</td>
<td>0.004</td>
<td>2.11,0.047*</td>
<td>0.0283</td>
<td></td>
<td>1.78,0.09</td>
<td>0.027</td>
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<tr>
<td>Supramarginal gyrus</td>
<td>-1.49,0.15</td>
<td>-0.009</td>
<td>-0.29,0.77</td>
<td>-0.05</td>
<td></td>
<td>-0.54,0.59</td>
<td>-0.10</td>
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</tbody>
</table>
## S6. Group differences in the lateralization index of cortical regions

<table>
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<tr>
<th></th>
<th>Cortical Thickness</th>
<th>Cortical surface area</th>
<th>Cortical volume</th>
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<tr>
<td></td>
<td>Controls</td>
<td>Psychosis</td>
<td>F, p</td>
</tr>
<tr>
<td></td>
<td>m±SE</td>
<td>m±SE</td>
<td></td>
</tr>
<tr>
<td>Pars opercularis</td>
<td>-0.012±0.007</td>
<td>-0.002±0.008</td>
<td>0.69,0.41</td>
</tr>
<tr>
<td></td>
<td>0.073±0.018</td>
<td>0.126±0.02</td>
<td>3.75,0.059</td>
</tr>
<tr>
<td>Pars triangularis</td>
<td>0.008±0.006</td>
<td>-0.01±0.006</td>
<td>4.33,0.043</td>
</tr>
<tr>
<td></td>
<td>-0.06±0.02</td>
<td>-0.09±0.02</td>
<td>1.67,0.21</td>
</tr>
<tr>
<td>Pars orbitalis</td>
<td>-0.004±0.008</td>
<td>0.006±0.008</td>
<td>0.72,0.40</td>
</tr>
<tr>
<td></td>
<td>-0.10±0.02</td>
<td>-0.11±0.02</td>
<td>0.021,0.89</td>
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<tr>
<td>STG</td>
<td>0.002±0.005</td>
<td>0.004±0.006</td>
<td>0.074,0.79</td>
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<tr>
<td></td>
<td>0.02±0.01</td>
<td>0.044±0.013</td>
<td>1.77,0.19</td>
</tr>
<tr>
<td>MTG</td>
<td>-0.002±0.006</td>
<td>0.004±0.006</td>
<td>0.45,0.51</td>
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<tr>
<td></td>
<td>-0.044±0.01</td>
<td>-0.07±0.014</td>
<td>1.80,0.19</td>
</tr>
<tr>
<td>ITG</td>
<td>0.013±0.005</td>
<td>0.004±0.006</td>
<td>1.39,0.24</td>
</tr>
<tr>
<td></td>
<td>0.05±0.01</td>
<td>0.03±0.01</td>
<td>2.40,0.13</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>-0.001±0.006</td>
<td>-0.007±0.006</td>
<td>0.44,0.51</td>
</tr>
<tr>
<td></td>
<td>0.02±0.02</td>
<td>-0.007±0.017</td>
<td>1.31,0.26</td>
</tr>
</tbody>
</table>

**Legend:** mean ± standard error reported; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus.
**S7. Post-hoc Investigation of Positive Symptoms**

Post-hoc analyses were conducted to investigate the relationship between any significant findings in the AF and associated cortical regions with the PANSS positive symptom total score and P3 of the PANSS which assesses hallucinatory behavior specifically. Furthermore, significant neuroanatomical associations with verbal cognition were further explored by separating the psychosis group into those who ever experienced auditory verbal hallucinations (AVH, n=9) and those who never experience AVHs (n=13). No significant associations were found between brain regions and positive symptoms ($r=-0.54$-$0.37, p=0.03$-$0.96$), however the significant association between the lateral index of the pars opercularis volume and verbal learning found in the psychosis group appeared to be driven by those who experienced AVH ($r=-0.91, p=0.004$), in comparison to those who never experienced AVHs ($r=-0.30, p=0.40$).

Verbal learning and verbal fluency (log) did not correlate with PANSS positive total score or P3 of the PANSS ($r=-0.32$-$0.21, p=0.23$-$0.94$).
GLOBAL BRAIN ESTIMATIONS AND SPEED OF PROCESSING DEFICITS IN PSYCHOSIS

Joanne Kenney1, Liam Kilmartin2, Shane McInerney1,3,4, Patrick Corcoran1, Cathy Scanlon1, Stefani O Donoghue1, Leila Nabulsi1, Sophia Arndt1, Elisabeth Scherz1, Alexander Leemans5, Ben Jeurissen6, Fintan Byrne1, Gareth J Barker7, Peter McCarthy8, Brian Hallahan1, Colm McDonald1, Dara M. Cannon1

1 Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway, H91 TK33, Galway, Ireland.
2 College of Engineering and Informatics, National University of Ireland, Galway
3 Department of Psychiatry, St Michaels Hospital, Toronto, Canada
4 Department of Psychiatry, University of Toronto, Canada
5 Images Sciences Institute, University Medical Centre Utrecht, The Netherlands
6 iMinds-Lab, University of Antwerp, Belgium
7 Institute of Psychiatry, Psychology and Neuroscience, London
8 Radiology, University Hospital Galway, Ireland

In preparation
ABSTRACT

Background: Impairments in speed of processing (SOP) are common in recent-onset psychosis. Due to the global operational nature of SOP, multiple brain regions are involved in successful SOP conduction. We aimed to investigate a range of global brain estimations to identify if global abnormalities are associated with SOP deficits in individuals in the early stage of psychotic illness.

Method: Twenty-six individuals with recent onset psychosis and 27 healthy controls underwent cognitive testing using the MATRICS Consensus Cognitive Battery and structural and diffusion-weighted MR scanning. Estimates of whole brain grey and white matter volume, global and local brain networks, global white matter anisotropy and the connectivity of the corpus callosum were examined in relation to SOP performance in both groups.

Results: In controls, longer global pathlength \( (r=0.43, p=0.049) \) was associated with SOP scores driven by the symbol coding (SC) component. Interhemispheric integration also related to SC in controls. Global pathlength related to the trail making test (TMT) \( (r=-0.43, p=0.042) \) in the psychosis group, as well as local network efficiency of the right inferior temporal gyrus \( (r=0.69, p=0.0003) \) and left parahippocampal gyrus \( (r=0.59, p=0.003) \) and anisotropy of the genu of the corpus callosum \( (r=0.55, p=0.007) \). Measures of SOP did not significantly relate to global grey and white matter volume, or a general factor of 9 white matter tracts.

Conclusion: In the current study, divergent associations of brain topology were found in controls and individuals with psychosis in processing speed and specific aspects of this measure. The primary investigation revealed that less integrated and efficient network topology and Interhemispheric integrity was associated with processing speed in controls, particularly with the symbol coding task identified post-hoc. In psychosis more integrated and efficient global and temporal lobe regions related to the trail making test subscale of processing speed as well as higher anisotropy of the genu. These contrasting findings in both groups may be indicative of pathology in the psychosis group who report reduced performance on these tests of processing speed.
INTRODUCTION

Deficits of cognition are prevalent in schizophrenia, in particular processing speed has been identified as being a prominent cognitive impairment in the disorder and has been identified as a central trait of cognitive deficits (Dickinson et al. 2007; Knowles et al., 2010). In a previous study, we identified a visuospatial and verbal index of processing speed to remain persistently impaired compared to other cognitive domains four years subsequent to presentation with a first episode of psychosis (Kenney et al., 2015). Other studies have also implicated a poorer trajectory for processing speed performance following an initial psychotic episode (Ayesa-Arriola et al., 2013, Juuhl-Langseth et al., 2014).

The magnitude of the processing speed deficit appears to be of substantial detriment to other cognitive domains (Leeson et al., 2010) as well as to overall intelligence. The processing speed hypothesis proposes that slower performance on this measure reduces the ability to process information automatically and effectively and contributes to deficits in a wide array of cognitive skills in psychosis (Rodriguez-Sanchez et al., 2007). In line with this theory, a number of studies have reported that processing speed contributes substantially to cognitive deficits such as working memory and attention (Kenney et al., 2015; Kelleher et al., 2013; Rodriguez-Sanchez et al., 2007, Ojeda et al., 2012). Processing speed deficits have also been identified as a potential endophenotype for schizophrenia (Antila et al., 2011, Alloza et al., 2015) and have been shown to be a possible marker for conversion to psychosis in high risk individuals (Gur et al., 2014; Seidman et al., 2010, Alloza et al., 2015) as well as relating to poorer functional outcome in psychosis (Leeson et al., 2010). Taken together, these findings reveal the necessity in uncovering the neuroanatomical substrates of processing speed impairments in psychosis.

As processing speed compliments a diverse range of cognitive abilities, successful operation of this skill is dependent upon coordinated activity from many distributed grey matter regions of the brain via the white matter tracts which connect them. Brain lesions located in multiple locations throughout the brain can result in processing speed impairments (DeLuca et al., 2004; Habekost & Rostrup, 2007). Due to the global operational nature of processing speed, this study aims to investigate a range of global estimations of the brain to examine whether abnormalities throughout the brain rather than at specific localised regions are associated with this cognitive deficit in psychosis.
As generalised grey and white matter of the brain have been found to be significantly reduced in schizophrenia and first-episode psychosis compared to control (Zipursky et al., 1998; Steen et al., 2006; White et al., 2011), firstly total grey and white matter volumes of the brain will be examined in relation to processing speed deficits. Secondly, schizophrenia has often been considered a dysconnectivity disorder (Friston et al., 1998), suggesting that aberrant connections between brain regions results in an inability to integrate neural information across distal brain regions and may underlie symptoms and cognitive impairments of the disorder (Stephan et al., 2006). This theory is supported by evidence of disconnection in a number of distinct white matter tracts across the brain (Pettersson-Yeo et al., 2011, Shenton et al., 2001; Wheeler & Voneskos, 2014). The next technique employed in the current study, network analysis, is a novel method to study global inter-connectedness of the whole brain which uses graph theory mathematics to describe the brain as a collection of nodes (grey matter regions) and edges (white matter tracts) (Rubinov et al., 2010; Friston et al., 1994). It can be used to further explore the disconnection hypothesis of schizophrenia in relation to impairments in cognition, specifically processing speed in the current study. Previous network analysis studies have related measures of global connectivity to intelligence in healthy individuals (Zalesky et al., 2011; Li et al., 2009), and processing speed performance in older adults (Wen et al., 2011). Measures such as global characteristic pathlength, global efficiency and global density which provide information about the segregation and integration of the brain network (O’ Donoghue et al., 2015) will be examined in relation to processing speed performance in the current study. Lastly, previous studies have found a common white matter factor to underlie a number of white matter tracts in the brain suggesting that there is a global phenomenon affecting many tracts as evidenced through their shared variance. Furthermore this general factor of white matter was related to intelligence and processing speed in older adults and individuals with schizophrenia (Alloza et al., 2015; Penke et al., 2010). Therefore, the current study will examine whether a common white matter factor underlies 9 tracts previously implicated in processing speed performance and how this factor relates to processing speed deficits in individuals with psychosis.

In addition to our global investigation of the brain in examining neural substrates of processing speed deficits, we finally explore the role of the corpus callosum in relation to these impairments. As dysconnectivity of the corpus callosum has been one of the most consistently reported findings in schizophrenia (Pettersson-Yeo et al., 2011, Holleran et al., 2014), and relates to processing speed impairments in individuals with bipolar...
disorder (Ajilore et al., 2015) an investigation of the microstructural organisation or anisotropy of the corpus callosum, (using a standard measure of anisotropy – fractional anisotropy, FA, and a novel tract-specific measure, hindrance modulated orientational anisotropy, HMOA) will be undertaken in relation to processing speed deficits in psychosis. To further investigate the range of connections passing through the corpus callosum, a novel network measure called interhemispheric integration will additionally be utilised. Previously, interhemispheric integrity has been related to processing speed in bipolar disorder (Ajilore et al., 2015).

Therefore, the overarching goal of Paper 3 is to investigate the neuroanatomical basis of variance in speed of processing in a control sample and related deficits in psychosis. While associations between specific brain regions and cognition have been reported, cognitive functions may not be the property of a single region of the brain but rather of an extended network of interactions between cortical regions. Therefore, global estimations of the whole brain network were chosen when investigating processing speed deficits. The decision to investigate measures of the whole brain was based on findings in the literature which suggest that the operational nature of processing speed is global in nature activating a widespread network of brain regions. Paper 1 of the current thesis supported the processing speed hypothesis (Kelleher et al., 2013; Rodriguez-Sanchez et al., 2007), which suggests processing speed deficits to be a core deficit in schizophrenia with the magnitude of this deficit contributing substantially to deficits in other cognitive domains (Leeson et al., 2010). Other studies have shown that a number of separate white matter tracts have been related to processing speed performance such as the corpus callosum (Karbasforoushan et al., 2015) and the superior and inferior longitudinal fasciculi (Turken et al., 2008). Additionally, age related decline in global white matter of the brain has been found to partially mediate processing speed decline (Salami et al., 2012), and illnesses which are characteristic of multiple lesions at various locations such as multiple sclerosis, show processing speed to be the primary cognitive deficit (DeLuca et al., 2004; Levine et al., 2006). Previously, processing speed performance in older adults was related to global connectivity of the brain and also related to 63 out of 68 individual nodes or regions of the brain investigated (Wen et al., 2011). Therefore, our hypotheses are based on these literatures which suggest that processing speed performance is global in nature and not localised to a specific brain region. While there is a limited literature investigating estimates of the global brain network and processing speed particularly in psychotic disorder as well as there being limited studies investigating network connectivity and cognition, we attempted to address this question by investigating
a number of measures of the global brain in relation to processing speed. Our objectives and hypotheses are summarised below:

**Objective 1a)** Network analysis investigating connectivity of the whole brain in relation to processing speed performance in controls and individuals with psychosis will be the primary investigation.

**Hypothesis 1a)** In healthy controls, global characteristic pathlength (CPL) will be negatively associated with the processing speed composite score, while inversely global efficiency will be positively associated with processing speed scores.

In individuals with psychosis, global characteristic pathlength (CPL) will be positively associated with the processing speed composite score, while inversely global efficiency will be negatively associated with processing speed scores.

Post-hoc exploratory analysis of the local efficiency of 29 nodes which have previously been related to processing speed will also be investigated in relation to the processing speed scores in both groups.

**Objective 1b)** Further exploratory network analysis will be conducted to investigate specifically the connectivity of regions which pass through the corpus callosum using network metrics, interhemispheric pathlength and interhemispheric efficiency.

**Hypothesis 1b)** We hypothesise that interhemispheric pathlength will be negatively associated with processing speed composite score and inversely interhemispheric efficiency will be positively associated with processing speed in psychosis. We hypothesise that the opposite direction of association will be evident in controls.

Post-hoc exploratory analysis of the microstructural organisation (HMOA, FA) of the corpus callosum and the processing speed composite score will be further conducted.

**Objective 2)** A secondary investigation of the paper will focus on a general white matter factor (FA) of 9 white matter tracts previously associated with processing speed performance.

**Hypothesis 2)** We hypothesise that a general white matter factor will be positively associated with processing speed composite score in the controls. In the individuals with psychosis, we hypothesise that there will be a negative association between general white matter and processing speed score.
**Objective 3)** A final investigation of global estimations of the brain will focus on global grey and white matter volume and the relationship with the processing speed composite score.

**Hypothesis 3)** In healthy controls, we hypothesise that global grey and white matter volume will be positively associated with processing speed.

As generalised grey and white matter of the brain has been reported to be reduced in schizophrenia, we hypothesise that a negative association will be evident between global grey and white matter and processing speed in psychosis.

**Post-hoc investigation**

Post-hoc exploratory investigations of the three subscales of the processing speed composite score (Trail Making Test – A; BACS- Symbol Coding and Verbal Fluency) will additionally be conducted with regards to the three specific objectives and hypotheses above.

**METHODS**

**Participants**

Twenty-six individuals with recent onset of psychotic illness and 27 healthy controls (HC) participated in the study (Table 1). Participants underwent cognitive testing and MR scanning at first-presentation of illness and four years later (follow-up), the latter time-point, which included a diffusion-weighted image acquisition, was used in the current analyses. All subjects were aged between 19 and 59 years. Diagnosis was determined using the Structured Clinical Interview for DSM-IV Research Version (SCID) (First et al., 2002; Association AP, 2000). The recruitment and clinical assessment of these individuals are described previously (Scanlon et al., 2014; McFarland et al., 2013). Exclusion criteria for all participants included neurological disorders (including epilepsy), comorbid substance or alcohol abuse in the last year, a history of head injury resulting in loss of consciousness for over 5 min, oral steroid use in the previous 3 months and general contraindications to MRI. Healthy controls were also excluded if they had a personal or family history of psychotic or affective disorder. The study was approved by the research
Ethics Committees of the National University of Ireland Galway and Galway University Hospital. Written informed consent was obtained from all participants.

Table 1. Demographic characteristics and clinical features of the study sample

<table>
<thead>
<tr>
<th></th>
<th>Recent –Onset Psychosis</th>
<th>Healthy Controls</th>
<th>Comparison (T/χ², p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Age (mean yrs±SD)</td>
<td>32±9</td>
<td>38±9</td>
<td>2.43, 0.02*</td>
</tr>
<tr>
<td>Gender N (m,f) (%fem)</td>
<td>16, 10 (31%)</td>
<td>15, 12 (20%)</td>
<td>0.20, 0.70</td>
</tr>
<tr>
<td>Education (mean yrs±SD)</td>
<td>16.1±2.8</td>
<td>17.3±3.4</td>
<td>1.43, 0.16</td>
</tr>
<tr>
<td>Handedness (left/right)</td>
<td>4/22</td>
<td>2/25</td>
<td>8.4, 0.36</td>
</tr>
<tr>
<td>Diagnosis (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizoaffective</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis NOS</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication (N)</td>
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<tr>
<td>Antipsychotics</td>
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<tr>
<td>Mood stabilizers</td>
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</tr>
<tr>
<td>Anti-depressants</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing information</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZ equivalents @ FU</td>
<td>202±281</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPZ equivalents total</td>
<td>245421±260750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms: PANSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>43.7±14.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive Score</td>
<td>10±3.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative Score</td>
<td>11.2±6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Score</td>
<td>22.6±6.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: SD = standard deviation, † = antipsychotic medication was converted to chlorpromazine equivalents (CPZ), (Lehman et al., 1998; Taylor et al., 2007; Woods, 2003); * = significant difference between groups in age, N = number, PANSS = positive and negative symptom scale (0-6 per item scale version), FU = follow-up.
Cognitive Measures

The MATRICS Consensus Cognitive Battery (MCCB) was administered to all individuals. The MATRICS Neurocognition Committee employed a rigorous process and procedure involving 130 scientists from across the field to decide upon 10 cognitive tests for inclusion in the MATRICS Consensus Cognitive Battery. The committee initially intended to include two types of measures in the Speed of Processing category; a verbal fluency measure and a graphomotor speed measure. The measures were psychometrically comparable in most respects. Initially, this domain included 4 subtests, 1) category fluency test, animal naming, 2) Trail Making Test, Part A, 3) Weschler Adult Intelligence Scale, 3rd ed (digit symbol coding subtest), 4) Brief Assessment of cognition in schizophrenia (BACS), symbol coding subtest. Brief Assessment of Cognition in Schizophrenia symbol coding subtest was selected because it showed a smaller practice effect than the WAIS-III digit symbol coding subtest. Given the brief administration time and high tolerability of these measures, the committee decided to include an additional graphomotor measure with a different format (the Trail Making Test, Part A) for a total of three tests (the Trail Making Test, Part A; the Brief Assessment of Cognition in Schizophrenia symbol coding subtest; and the category fluency test).

Raw scores of the cognitive tests were age and gender corrected using the MCCB computerized program, and converted to T-scores, which were then used in all subsequent statistical analyses. Normative data were obtained from administering the battery to 300 individuals across five sites in the U.S. (Kern et al., 2008) stratified into three age ranges and accounting for gender and education.

The Speed of Processing composite score was used for the primary investigation, it is highly correlated with all individual subscales in our sample (Table 2). Post-hoc investigations of the three subscales of the composite score were additionally investigated. A high correlation between individual subscales of the speed of processing domain is also evident (Table 2).
Table 2: Correlations between speed of processing composite score (SOP) and individual subscales Trail Making Test, part A (TMT), Brief Assessment of Cognition in Schizophrenia- Symbol Coding (SC), and category fluency test, animal naming (VF) (see Kenney et al., (2015) for description of cognitive tests). All subjects (individuals with psychosis and healthy controls) included (n= 53).

<table>
<thead>
<tr>
<th></th>
<th>SOP</th>
<th>TMT</th>
<th>SC</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOP</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT</td>
<td>r=0.85,p=2.34E-15</td>
<td>1</td>
<td>r=0.65,p=2.3 E-7</td>
<td>r=0.675,p=5.5E-8</td>
</tr>
<tr>
<td>SC</td>
<td>r=0.89,p=1.1 E-18</td>
<td>r=0.65,p=2.3 E-7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>r=0.82,p=2.35E-13</td>
<td>r=0.675,p=5.5E-8</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

MRI Acquisition

All subjects underwent structural and diffusion MR imaging at University Hospital Galway (UHG) in a 1.5 Tesla Siemens Magnetom Symphony scanner (Erlangen, Germany) equipped with a 4-channel head coil. A volumetric T1-weighted magnetization-prepared rapid acquisition of gradient echo (MPRAGE) sequence was acquired with the imaging parameters: Repetition time (TR): 1140 ms, echo time (TE): 4.38 ms, inversion Time (TI): 600 ms, flip angle 15°; matrix size 256 x 256; an in-plane pixel size of 0.9 mm x 0.9 mm and slice thickness of 0.9 mm. Whole brain high angular resolution data was obtained in the axial orientation along 64 independent diffusion gradient directions, b-value = 1300 s/mm², with 7 reference non-diffusion-weighted images (b-value = 0 s/mm²). Image parameters were: echo time (TE) = 95 ms, repetition time (TR) = 8100 ms, flip angle = 15°, voxel size = 2.5 mm³, matrix size= 96 x 96, slice thickness = 2.5 mm, in-plane resolution = 2.5 mm².

Image processing – Structural MR Image Processing and Quality Control

Intensity inhomogeneities in the T1-weighted images were corrected using nonparametric, non-uniform intensity normalization (N3) (Sled et al., 1998). Image processing was carried out using FreeSurfer, stable version 5.1 (https://surfer.nmr.mgh.harvard.edu). Detailed
descriptions of this method have already been reported (Scanlon et al., 2014; Dale et al., 1999; Fischl B, 1999), but are briefly summarized below. Based on a linear combination of voxel intensities and local geometric constraints, the cerebral white matter (WM) is first segmented, divided into 2 hemispheres, and the brain stem and cerebellum removed. Tessellation is then performed on the WM surface and refined to alleviate the voxel-based nature of the initial curvature. The WM surfaces are deformed outward to generate the pial (GM/CSF intersection) surface. Topologic defects in the surface are corrected using an automated topology fixer. Visual quality checks were then performed and inaccuracies were manually edited and corrected by reprocessing. Total grey matter volume, a summation of subcortical grey matter, left and right hemisphere cortex and cerebellum grey matter, and total white matter volume were extracted. Intracranial volume was also extracted in order to normalize whole brain volumes in relation to head size.

**Image processing – Diffusion MR Image Processing and Quality Control**

Explore DTI (version 4.8.4) was used to correct for motion and eddy current induced geometric distortions including rotation of the b-matrix to preserve the orientation information (Leemans et al., 2009a; Leemans et al., 2009b). Data quality was further assessed by visual inspection (Tournier et al., 2007). Robust estimation of the diffusion tensor was implemented using the RESTORE approach (Chang et al., 2005). Whole brain tractography was carried out in Explore DTI using the constrained spherical deconvolution (CSD) tracking algorithm (Jeurissen et al., 2014) with recursive calibration of the response function (Tax et al., 2016). Fibre pathways were reconstructed in each voxel and continued with a step size of 1mm until the fibre tract entered a voxel with FA < 0.20 or made a high angular turn (angle > 30 degrees).

**Network analysis**

Weighted and undirected 90x90 connectivity matrices were generated for each subject by combining the whole brain tractography using average Fractional anisotropy (FA) and number of streamlines (NOS) weighting and cortical and subcortical parcellated structures. The Automated Anatomical Labelling Atlas (AAL-90) (Tzourio-Mazoyer et al., 2002) was implemented for parcellating cortical and subcortical structures into 90 brain regions (45 bilaterally). FA weighting defines the level of white matter anisotropic diffusion in brain voxels, while number of streamlines provides information about the quantity and strength of connections between brain regions (Van Heuval et al., 2011). *Nodes* of the network
represent grey matter regions, while edges represent the white matter tracts between those regions. To reduce false-positive reconstruction of streamlines, connectivity matrices were thresholded at a density value of 0.2 (Fornito et al., 2012).

Using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010), the following global network metrics were generated: (i) global characteristic pathlength (the average shortest pathlength of the network and a common measure of functional integration) (ii) global efficiency (the average inverse shortest pathlength) and (iii) global density (the total number of edges of a network as a proportion of the total number of possible edges connecting the same number of nodes).

For further local nodal analysis, 29 bilateral regional nodes were selected based on these regions being previously implicated in processing speed cognitive tasks (Wen et al., 2011, Tourotoglou et al., 2012, Dobryakva et al., 2015; Genova et al., 2009) (Table 2). False discovery rate (FDR) correction for the 29 regions was implemented to correct for multiple comparisons (Supplementary S1).

**Interhemispheric and Intrahemispheric Integration/ Tract Definition of the Corpus Callosum**

Based on previous definitions (Highly et al., 1999) and Mori’s Atlas of Human White Matter (Mori et al., 2005), the genu, body and splenium of the corpus callosum were isolated from whole brain tractography. AND gates and NOT gates were manually placed on directional encoded colour fractional anisotropy (DEC-FA) maps. AND gates were placed on three sagittal slices to encompass the white matter of the corpus callosum one on the midsagittal plane and two AND gates parasagittal to this gate, a half voxel outside the tract boundaries(Figure 1). NOT gates were added to remove spurious tracts. The segment defined by the AND gates was included only in analysis. The genu, body and splenium of the corpus callosum were separately isolated based on Mori’s white matter atlas. AND gates were placed sagittally on the mid-sagittal slice to divide the tract into the 3 regions (See figure 2). Two measures of anisotropy (median hindrance modulated orientational anisotropy - HMOA and median fractional anisotropy - FA) were extracted for each segment.

Based on Leow et al., (2013), we further investigated the corpus callosum in relation to the brain network it connects. Intra/inter-hemispheric pathlength and efficiency metrics were created based on the definition of global characteristic pathlength (CPL) and global
efficiency (Leow et al., 2013) and based on division of the 90 node brain network into two modules representing the two hemispheres, consisting of 45 nodes each. The intrahemispheric pathlength is characterised by the average shortest path length between nodes within each module or hemisphere. Interhemispheric pathlength is defined as the average shortest path length between a node in one module and nodes in the contralateral module. Intra/inter-hemispheric efficiency represents the inverse of the two previous metrics described.
Figure 1. Mid-sagittal and two para-sagittal AND gates were placed on the DEC-FA map to isolate the corpus callosum.

Figure 2. AND gates placed on the DEC-FA maps to isolate the genu (A), body (B) and splenium (C) of the corpus callosum.
General White Matter Factor- Atlas based ROI Analysis

Automated atlas based analysis was conducted using Explore DTI as previously implemented in Kersbergen (2014). The atlas template (International Consortium for Brain Mapping (ICBM) DTI-81 atlas; Maziotta et al., 2001) was warped to each individual data set (motion distortion and eddy current corrected diffusion images) and FA extracted for each region of interest selected. The ICBM atlas is a probabilistic white matter atlas that combines DTI white matter information with the anatomical template, ICBM-152.

Nine white matter regions which have previously been associated with tasks of processing speed were selected for analysis. The genu, body and splenium of the corpus callosum and bilateral cingulum and uncinate fasciculus were included as they were identified as being related to processing speed (Penke et al., 2010), as was bilateral superior longitudinal fasciculus, a tract suggested to be prominently involved in digit symbol performance, a visuospatial measure of processing speed (Turken, 2009).

Adopting a recent approach described by Penke et al., (2010) and Alloza et al., (2015), principal component analysis (PCA) was conducted using IBM SPSS (v.21) on the FA of the 9 white matter regions. Partial correlation was used to study associations between the FA general factor and the processing speed composite score, with post-hoc analysis on the three individual measures of processing speed (TMT, BACS-SC, VF), controlling for age and gender.

Statistics

All statistics were conducted using IBM SPSS (v.21). Shapiro–Wilk tests were used to test for normal distribution of each variable, summarised in supplementary S2.

Partial correlation analyses were implemented for the psychosis group and the healthy controls when investigating the relationship between brain measures and processing speed cognitive variables. Tract volume was covaried for in analyses of FA, and ICV was also added as a covariate in total brain volume analyses. The processing speed composite score was used in primary correlation investigations, with post-hoc analyses of the three individual measures of processing speed (TMT, symbol coding and verbal fluency). Age and gender were covaried for in all analyses. Uncorrected p-values are reported only.
RESULTS

Group differences in Speed of Processing Performance

Individuals with psychosis displayed significantly reduced performance compared to healthy controls on the speed of processing (SOP) composite score and the three constituent measures of this composite score - TMT-A and Symbol coding and verbal fluency (Table 3).

Table 3. Individuals with psychosis had significantly poorer performance compared to healthy controls on all measures of processing speed.

<table>
<thead>
<tr>
<th>Cognitve Test</th>
<th>Healthy Control</th>
<th>Individuals with Psychosis</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of processing *</td>
<td>57.16±2.19</td>
<td>38.6±2.24</td>
<td>33.</td>
<td>0.0001</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td>54.24±2.15</td>
<td>39.1±2.24</td>
<td>22.</td>
<td>0.00019</td>
</tr>
<tr>
<td>BACS-SC</td>
<td>57.37±2.13</td>
<td>38.05±2.38</td>
<td>27.</td>
<td>0.0004</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>1.75±0.02</td>
<td>1.66±0.02</td>
<td>11.</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: adjusted means (means corrected for age and gender) ± standard error reported; BACS –SC = Brief assessment of cognition in schizophrenia: Symbol coding, * composite score of following three measures.

Figure 3. Bar chart of the group differences on cognitive measures.
Global and local brain networks in relation to speed of processing performance

In partial support of hypothesis 1, using number of streamline weighting, a significant association was found in the controls between global CPL (r=0.43, p=0.049) and the processing speed composite score (Figure 4A), however in the opposite direction to that hypothesised. This finding appears to be explained primarily by the symbol coding component of the composite measure which related significantly to global CPL (r=0.49, p=0.02) and global efficiency (r=−0.51, p=0.017) (Figure 4B & 4C). Streamline weighting also revealed a significant association in the psychosis group between the trail making tests (TMT) and global CPL (r=−0.43, p=0.042) (Figure 4D). There were no further significant relationships evident in either group between cognition and global measures using FA or number of streamline weighting (Supplementary S3 & S4).
Figure 4. Using number of streamline weighting, speed of processing (SOP) composite score was significantly related to global characteristic pathlength (CPL) in controls (A), driven by the relationship with symbol coding (BAC-SC) (B). Significant associations were also present between symbol coding and global efficiency in controls (C) and between the trail making test and Global CPL.
in the psychosis group (D). * Significant correlations. Corresponding non-significant associations found in psychosis group and controls are shown in the right panel.

When investigating regional efficiency of the 29 nodes, local efficiency (FA) of the right inferior temporal gyrus ($r=0.69, p=0.0003$) and the left parahippocampal gyrus ($r=0.59, p=0.003$) was positively associated with the TMT in the psychosis group (Figure 5). No further significant associations using either FA or streamline weighting were found between cognitive scores and any other local node investigated, surviving multiple comparisons correction, (controls: $r=-0.37\text{-}0.54, p=0.006\text{-}0.98$; psychosis: $r=-0.57\text{-}0.28, p=0.004\text{-}0.96$).

**Figure 5.** For the individuals with psychosis, higher local efficiency in the right inferior temporal gyrus and left parahippocampal gyrus was associated with better performance on a visuospatial measure of processing speed (Trail Making Test – Part A).

**Interhemispheric Integrity/Corpus callosum in relation to speed of processing performance**

Investigations of intra- and inter-hemispheric integration revealed, using FA weighting, an association between interhemispheric efficiency ($r=-0.42, p=0.046$) and symbol coding and with interhemispheric pathlength and symbol coding ($r=0.42, p=0.046$) in controls (Figure 7A & 7B). Also, using streamline weighting, a significant relationship was found between interhemispheric efficiency and symbol coding in the healthy controls ($r=-0.46, p=0.026$) (Figure 7C). No other significant associations were found between measures of integration and any cognitive measures (Supplementary S3 & S4).
Figure 7. Using FA weighting, lower interhemispheric efficiency and higher characteristic pathlength (CPL) were significantly associated with symbol coding in the control group. Using streamline weighting, lower Interhemispheric efficiency was significantly related to symbol coding in controls. * Significant correlations. Corresponding non-significant associations found in psychosis and controls are shown in the right panel.
Investigations of the corpus callosum revealed a significant positive correlation between FA of the genu and the Trail Making Test \((r=0.55, p=0.007)\) was found in the psychosis group (Figure 6). No further significant associations were evident between any remaining cognitive measures and anisotropy of the corpus callosum in the psychosis group (HMOA: \(r=-0.32-0.04, p=0.13-0.99\); FA: \(r=-0.34-0.27, p=0.12-0.53\) ) or controls (HMOA: \(r=-0.21-0.12, p=0.32-0.99\); FA: \(r=-0.19-0.36, p=0.09-0.95\)). For results of correlations with individual cognitive measures see Supplementary S10.

**Figure 6.** FA in the genu of the corpus callosum was positively associated with scores on the trail making test (TMT) in individuals with psychosis.

**General white matter factor in relation to speed of processing performance**

Explorations of a general white matter factor in the 9 tracts investigated revealed a clear principal component in the healthy controls for the first unrotated component explaining 53\% of the variance among all white matter tracts. Loadings and scree plots are presented in Supplementary S6 and S8. The individuals with psychosis showed 3 principal components explaining the variance in white matter. However, the first component explained 52\% of the variance (eigenvalue = 4.41), with components 2 (eigenvalue = 1.35) and 3 (eigenvalue = 1.30) contributing an additional ~15\% of variance each. Therefore, the first principal component was used in the analysis. See Supplementary Table S7 and S9 for loadings and scree plots. However, no significant correlations between the white matter general factor and any of the processing speed cognitive tests were found in the controls \((r=-0.22-0.29,\)
Global Grey and White matter in relation to speed of processing performance

Total grey and white matter volumes did not significantly relate to cognition in either group (GM: r=-0.05-0.32, p=0.16-0.81; WM: r=-0.20-0.14, p=0.39-0.77), therefore not supporting hypothesis 3.
DISCUSSION

The current study performed analysis on a range of global brain estimates using complementary neuroimaging approaches as well as a detailed investigation of the corpus callosum. Specifically, we aimed to address whether abnormalities in global brain connectivity, global brain volume, and global white matter are involved in impairments of processing speed in individuals with psychosis. As aberrances in the corpus callosum are widely reported in schizophrenia and relate to processing speed performance in psychotic disorders (Ajilore et al., 2015), we further addressed whether anomalies in the microstructural organization of this tract as well as in the connections which pass through the corpus callosum are contributory factors to deficits of processing speed.

The study found associations between global network topology and the processing speed composite score in the healthy controls. Post-hoc analysis revealed this association was driven by the symbol coding component of this composite measure. Interpretation of these relationships suggests that longer pathlengths and reduced global efficiency appear beneficial for processing speed performance in controls particularly visuo-spatial aspects, as indexed by symbol coding. No corresponding relationships were found between global connectivity and the composite score in the individuals with psychosis, which may be indicative of pathology in this group. Interpretation of these sophisticated mathematical graph theory metrics in relation to cognition and brain systems is complex and ambiguous as of yet (Ajilore et al., 2015), as a limited number of studies have directly related structural network measures to cognition, highlighted by Van Heuval et al. (2010). Traditional definitions of graph theory would suggest that networks with lower efficiency represent an inversion of a less integrated brain system and characteristic of poorer networks (Leow et al., 2013). However, conceptually relating the brain system to a mathematical network may not be interchangeable and interpretations must be taken with caution until further research is conducted. Alternative explanations may exist, such that lower efficiency may relate to a reduced level of information processing throughout the network which may be ideal for some aspects of cognition. Lower efficiency in functional networks have appeared of benefit to more difficult cognitive tasks in both controls and individuals with first-episode schizophrenia (Fornito et al., 2011). Attempting to interpret the benefit of a longer pathlength to symbol coding scores found in this study is perplex; it is possible that using pathlengths as a main measure of integration may not truly represent the network as it does not take into account how the path embeds in the rest of the network – for example, if large number of connections are attached to a node on the
shortest path, functional connectivity may be reduced, or if along a given path, branch points exist this may also lead to reduced functional connectivity due to dispersion of the signal (Goni et al., 2013). Therefore, structurally a shorter pathlength represented mathematically may not completely map onto the functional signals, and interpretations in relation to cognition becomes partial insufficient. Until further work is complete, interpretation of our findings remains ambiguous.

While no associations were reported between connectivity metrics and the primary investigation of the processing speed composite score in the psychosis group, post-hoc investigations of subscales revealed lower global pathlength to be related to a visual spatial aspect of processing speed, the trail making test (TMT). Investigations of connectivity in local brain regions also revealed associations between specific nodes and the TMT; higher efficiency of the right inferior temporal gyrus (ITG) and the left parahippocampal gyrus were positively associated with this test, which was not correspondingly found in controls. Taken together these findings may be indicative of impairment in global connectivity and particularly temporal lobe connectivity contributing to the poor performance on this task in psychosis. In schizophrenia, impaired connectivity has previously been reported in the temporal lobe where both the ITG and parahippocampal gyrus are located (Zalesky et al., 2012) and an increased hub role of temporal regions has been suggested to occur as compensation for decreased hub-functioning of frontal regions in the disorder (Van-Heuval et al., 2010). Additionally, reduced network homogeneity in right middle temporal gyrus has been noted in drug-naive first episode schizophrenia (Guo et al., 2014). While several studies suggest abnormalities in temporal structures such as the superior and middle temporal gyrus in schizophrenia, few have focused on other temporal lobe structures such the ITG and parahippocampal gyrus. Of the few studies investigating these structures findings are incongruous, with some reporting abnormal volume (Shenton et al., 2001; Onitsuka et al., 2004, Kuroki et al., 2006) and others finding no differences compared to controls (Takahashi et al., 2006), although the right middle ITG has previously been linked to psychotic symptoms (Kuroki et al., 2006). In terms of cognitive functioning, both the ITG and parahippocampal are involved in visual processing or visual recognition (Goh et al., 2007; Aminoff et al., 2013; Ishai et al., 1999; Herath et al., 2001) amongst other functions such as memory. Therefore the link with a visuo-spatial task of processing speed found in this study is plausible. Future studies may specifically investigate sub-networks involving these temporal lobe structures in relation to visuo-spatial aspects processing speed deficits in psychosis.
A global phenomenon as indexed by a common white matter factor was found to underlie a range of white matter tracts in both controls and individuals with psychosis similar to previous reports (Penke et al., 2010; Alloza et al., 2015). This common factor suggests that the microstructural organization of each tract is closely positively associated with organization in all other tract. It has been suggested that pathophysiological factors that affect white matter tracts may do so in a global manner rather than focused on regional tracts, thereby supporting global disconnection theories of schizophrenia. However, the current study did not find an association between general white matter factors and cognition unlike previous studies of older adults and schizophrenia (Penke et al., 2010; Alloza et al., 2015), potentially due to the early stage of illness investigated. Additionally methodological differences between the studies may contribute to our lack of significant association with cognition, such as contrasting choices of atlas and white matter tracts included in analysis. Both Penke et al. (2010) and Alloza et al. (2015) investigated mainly general reaction time tests of processing speed with no verbal processing speed tasks, therefore global white matter may be more strongly related with simple reaction time indices of processing speed.

Our final targeted investigation of the corpus callosum, revealed a positive association between FA of the genu of the corpus callosum and Trail Making Tests scores in individuals with psychosis, with no relationship evident in controls. Similarly, the genu and body of the corpus callosum have previously been related to a range of processing speed tasks in bipolar disorder (Ajilore et al., 2015). Interhemispheric integration, using FA and streamline weighting, was significantly related to symbol coding in controls which was not present in the psychosis group. Ajilore et al., (2015) found a positive association between interhemispheric integration and processing speed scores in individuals with bipolar, such that increased efficiency and correspondingly lower pathlength related with performance. However, in our healthy control sample the opposite direction of results was evident suggestive of reduced efficiency being more beneficial for cognitive performance. The contrasting direction of associations may indicate divergent patterns of connectivity being involved in processing speed performance in individuals with psychotic disorder and healthy individuals. However, as mentioned previously, interpretation of the direction of these metrics in relation to cognition remains ambiguous.

Strengths of the current study include a comprehensive investigation of global brain estimates in psychosis in attempting to uncover neuroanatomical contributions to deficits.
of processing speed. Novel aspects of this study were that we investigated cortico-subcortico connectivity as subcortical nodes (such as hippocampus, amygdala, caudate) are known to be implicated in psychotic disorders. To our knowledge, this is the first study to investigate network measures in relation to processing speed in psychosis and additionally the first to investigate interhemispheric integration in this cohort. Limitations of the study include a small sample size which may limit the statistical power of analysis particularly in the principal component analysis. When constructing the connectivity matrices the connection-to-length mapping involved an element-wise inverse mapping which may be too limiting when investigating the large range of streamlines in the streamline weighting matrices.

CONCLUSION

In the current study, we report divergent associations of brain topology in relation to cognition in healthy controls and individuals with psychosis. Increased segregation of global brain connections related to processing speed in controls, particularly in symbol coding tasks which also related to increased segregation of interhemispheric connections. The absence of a corresponding relationship in the psychosis group may be indicative of abnormalities in the brain connectivity involved in these aspects of cognition in psychosis. In the psychosis group, more integrated and correspondingly higher efficient network topology related to trail making test scores both globally and in temporal regions. Increased anisotropy in the genu of the corpus callosum also related to trail making test performance. These patterns of connectivity in the psychosis group, which are incongruent with controls, may not be conducive to successful cognitive performance as they perform significantly lower than controls on this test of processing speed. Further studies are recommended to assist in interpretation of the graph metrics in relation to cognitive performance.
REFERENCES


SUPPLEMENTARY MATERIAL

S1: Twenty-nine bilateral cortical regions were selected for their involvement in processing speed tasks. The local efficiency of these regions was investigated in relation to processing speed performance.

<table>
<thead>
<tr>
<th>Cortical Region</th>
<th>Cortical Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Precentral Gyrus</td>
<td>16. Superior Occipital Gyrus</td>
</tr>
<tr>
<td>2. Superior Frontal Gyrus</td>
<td>17. Middle Occipital Gyrus</td>
</tr>
<tr>
<td>4. Middle Frontal Gyrus</td>
<td>19. Fusiform Gyrus</td>
</tr>
<tr>
<td>5. Middle Orbito-Frontal Gyrus</td>
<td>20. Postcentral Gyrus</td>
</tr>
<tr>
<td>7. Inferior Frontal Gyrus – Pars Triangularis</td>
<td>22. Inferior Parietal Lobule</td>
</tr>
<tr>
<td>8. Supplementary Motor Area</td>
<td>23. Supramarginal Gyrus</td>
</tr>
<tr>
<td>9. Insula</td>
<td>24. Precuneus</td>
</tr>
<tr>
<td>10. Anterior Cingulate Gyrus</td>
<td>25. Paracentral Lobule</td>
</tr>
<tr>
<td>12. Parahippocampal Gyrus</td>
<td>27. Superior Temporal Pole</td>
</tr>
<tr>
<td>13. Calcarine Sulcus</td>
<td>28. Middle Temporal Pole</td>
</tr>
<tr>
<td>15. Lingual Gyrus</td>
<td></td>
</tr>
</tbody>
</table>
S2. Results of Normal distribution Tests using Shapiro-Wilks

**Cognition:** Speed of processing composite score, Trail Making Test (TMT) and symbol coding (BACS-SC) were all normally distributed (w=0.98-0.99, p=0.84-0.97). Fluency scores were not normally distributed (w=0.93, p=0.006), but became so following log transformation (w=0.97, p=0.16) which was used in all analysis thereafter.

**Whole Brain:** Whole brain grey matter (w=0.98, p=0.41) and white matter (w=0.98, p=0.38) were normally distributed. For network measures indexed by both FA and number of streamlines, CPL, global efficiency and global density were all normally distributed (w=0.96-0.97, p=0.07-0.49), local nodes were also normally distributed for both weighted indices. Global efficiency (FA) and CPL (number of streamlines) were not normally distributed (w=0.79, p=0.00; w=0.90, p=0.00 respectively) but became so following removal of one outlier in each (w=0.98, p=0.41; w=0.98, p=0.49). Outliers were identified as p>0.05 and >3sd away from the mean.

**Corpus callosum:** Measures of intrahemispheric pathlength and efficiency (FA and number of streamlines) were normally distributed in both hemispheres (left: w=0.97-0.99, p=0.13-0.76; right: w=0.96-0.99, p=0.05-0.76). Additionally, interhemispheric pathlength (FA and number of streamlines) was normally distributed (w=0.97-0.98, p=0.06-0.40). The FA of the genu, body and splenium of the corpus callosum and HMOA of the body and splenium were normally distributed (w=0.97-0.98, p=0.24-0.69). HMOA of the genu was not normally distributed (w=0.88, p=0.00009). Spearman’s non-parametric correlational analysis was carried out for the measure and Kruskal-Wallis when examining group differences.
S 3: Associations between global network measures (FA) and cognitive measures of processing speed in healthy controls and individuals with psychosis.

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th></th>
<th></th>
<th></th>
<th>Individuals with Psychosis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOP</td>
<td>TMT</td>
<td>BACS-SC</td>
<td>VF</td>
<td>SOP</td>
<td>TMT</td>
<td>BACS-SC</td>
<td>VF</td>
</tr>
<tr>
<td>Global CPL</td>
<td>-0.13,0.55</td>
<td>-0.19,0.38</td>
<td>-0.23,0.31</td>
<td>0.16,0.49</td>
<td>-0.26,0.23</td>
<td>-0.37,0.09</td>
<td>-0.19,0.37</td>
<td>-0.04,0.85</td>
</tr>
<tr>
<td>Global Eff</td>
<td>0.12,0.59</td>
<td>0.19,0.41</td>
<td>0.22,0.33</td>
<td>-0.16,0.48</td>
<td>0.30,0.17</td>
<td>0.41,0.055</td>
<td>0.23,0.29</td>
<td>0.09,0.69</td>
</tr>
<tr>
<td>Global Density</td>
<td>-0.22,0.32</td>
<td>-0.29,0.19</td>
<td>-0.25,0.27</td>
<td>-0.03,0.88</td>
<td>-0.14,0.51</td>
<td>-0.21,0.34</td>
<td>-0.22,0.32</td>
<td>0.07,0.73</td>
</tr>
<tr>
<td>Local RITG Eff</td>
<td>0.15,0.52</td>
<td>0.23,0.30</td>
<td>0.15,0.50</td>
<td>-0.11,0.64</td>
<td>0.56,0.006</td>
<td>0.69,0.0003</td>
<td>0.4,0.05</td>
<td>0.22,0.31</td>
</tr>
<tr>
<td>Local LParaH Eff</td>
<td>-0.03,0.89</td>
<td>0.12,0.59</td>
<td>0.16,0.47</td>
<td>-0.31,0.17</td>
<td>0.49,0.019</td>
<td>0.59,0.003*</td>
<td>0.39,0.06</td>
<td>0.08,0.71</td>
</tr>
<tr>
<td>InterHemispheric CPL</td>
<td>-0.31,0.17</td>
<td>-0.22,0.32</td>
<td>-0.42,0.046*</td>
<td>-0.08,0.72</td>
<td>0.04,0.86</td>
<td>-0.12,0.59</td>
<td>0.11,0.62</td>
<td>0.07,0.75</td>
</tr>
<tr>
<td>InterHemispheric EFF</td>
<td>0.29,0.19</td>
<td>0.19,0.41</td>
<td>0.42,0.046*</td>
<td>0.09,0.68</td>
<td>-0.04,0.84</td>
<td>0.11,0.62</td>
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<tr>
<td>IntraHemispheric CPL Left</td>
<td>0.02,0.94</td>
<td>-0.16,0.48</td>
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<td>0.29,0.19</td>
<td>0.03,0.91</td>
<td>-0.32,0.13</td>
<td>0.19,0.39</td>
<td>0.16,0.47</td>
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<tr>
<td>IntraHemispheric EFF Left</td>
<td>-0.002,0.99</td>
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<td>-0.28,0.20</td>
<td>0.01,0.97</td>
<td>0.36,0.09</td>
<td>-0.15,0.49</td>
<td>-0.14,0.53</td>
</tr>
<tr>
<td>IntraHemispheric CPL Right</td>
<td>-0.17,0.45</td>
<td>-0.29,0.19</td>
<td>-0.19,0.38</td>
<td>0.14,0.55</td>
<td>-0.10,0.64</td>
<td>-0.30,0.16</td>
<td>0.02,0.94</td>
<td>0.06,0.79</td>
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<tr>
<td>IntraHemispheric EFF Right</td>
<td>0.16,0.47</td>
<td>0.27,0.22</td>
<td>0.17,0.46</td>
<td>-0.11,0.61</td>
<td>0.12,0.59</td>
<td>0.35,0.09</td>
<td>0.001,0.99</td>
<td>-0.09,0.69</td>
</tr>
</tbody>
</table>

**Legend:** SOP = composite processing speed score; TMT = Trail Making Test: Part A; BACS-SC = Brief Assessment of Cognition in Schizophrenia: Symbol Coding; VF = Verbal Fluency scores (log transformed); CPL = characteristic pathlength; Eff = efficiency; RITG = right inferior temporal gyrus; LParaH = left parahippocampus. * = significant correlations.
**S4:** Associations between global network measures (number of streamlines) and cognitive measures of processing speed in healthy controls and individuals with psychosis.

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Individuals with Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Streamlines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOP</td>
<td>TMT</td>
</tr>
<tr>
<td>Global CPL</td>
<td>0.41,0.049*</td>
<td>0.28,0.21</td>
</tr>
<tr>
<td>Global Eff</td>
<td>-0.42,0.056</td>
<td>-0.27,0.22</td>
</tr>
<tr>
<td>Global Density</td>
<td>-0.22,0.32</td>
<td>-0.29,0.20</td>
</tr>
<tr>
<td>Local RITG Eff</td>
<td>0.009,0.97</td>
<td>0.09,0.68</td>
</tr>
<tr>
<td>Local LParaH Eff</td>
<td>0.08,0.73</td>
<td>0.25,0.26</td>
</tr>
<tr>
<td>InterHemispheric CPL</td>
<td>0.35,0.11</td>
<td>0.32,0.15</td>
</tr>
<tr>
<td>InterHemispheric EFF</td>
<td>-0.37,0.09</td>
<td>-0.35,0.11</td>
</tr>
<tr>
<td>IntraHemispheric CPL Left</td>
<td>0.19,0.38</td>
<td>0.20,0.37</td>
</tr>
<tr>
<td>IntraHemispheric EFF Left</td>
<td>-0.17,0.45</td>
<td>-0.17,0.46</td>
</tr>
<tr>
<td>IntraHemispheric CPL Right</td>
<td>0.30,0.18</td>
<td>0.24,0.29</td>
</tr>
<tr>
<td>IntraHemispheric EFF Right</td>
<td>-0.32,0.15</td>
<td>-0.28,0.21</td>
</tr>
</tbody>
</table>

**Legend:** SOP = composite processing speed score; TMT = Trail Making Test: Part A; BACS-SC = Brief Assessment of Cognition in Schizophrenia: Symbol Coding; VF = Verbal Fluency scores (log transformed); CPL = characteristic pathlength; Eff = efficiency; RITG = right inferior temporal gyrus; LParaH = left parahippocampus. * = significant correlations.
S5. Correlations between the general white matter factor and performance on processing speed composite score and subscales in controls and individuals with psychosis

<table>
<thead>
<tr>
<th></th>
<th>SOP r,p</th>
<th>TMT r,p</th>
<th>BACS-SC r,p</th>
<th>VF r,p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Factor – controls</strong></td>
<td>-0.02,0.92</td>
<td>0.08,0.71</td>
<td>0.09,0.65</td>
<td>-0.22,0.29</td>
</tr>
<tr>
<td><strong>General Factor - psychosis</strong></td>
<td>-0.25,0.25</td>
<td>-0.18,0.42</td>
<td>-0.21,0.34</td>
<td>-0.31,0.15</td>
</tr>
</tbody>
</table>

**Legend:** SOP = speed of processing composite score; TMT = trail making test; BACS-SC = brief assessment of cognition in schizophrenia – symbol coding; vf = verbal fluency.
56. **Individual white matter tracts and their corresponding loadings for the general white matter factor for the healthy control group**

<table>
<thead>
<tr>
<th>White matter tract</th>
<th>Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Corpus callosum</td>
<td>0.86</td>
</tr>
<tr>
<td>Splenium Corpus callosum</td>
<td>0.86</td>
</tr>
<tr>
<td>Genu Corpus callosum</td>
<td>0.78</td>
</tr>
<tr>
<td>Left Cingulum (cingulate gyrus)</td>
<td>0.73</td>
</tr>
<tr>
<td>Right Cingulum (cingulated gyrus)</td>
<td>0.67</td>
</tr>
<tr>
<td>Left Superior longitudinal fasciculus</td>
<td>0.90</td>
</tr>
<tr>
<td>Right Superior longitudinal fasciculus</td>
<td>0.68</td>
</tr>
<tr>
<td>Left uncinate fasciculus</td>
<td>0.94</td>
</tr>
<tr>
<td>Right uncinate fasciculus</td>
<td>0.94</td>
</tr>
</tbody>
</table>

57. **Individual white matter tracts and their corresponding loadings for the general white matter factor for the individuals with psychosis**

<table>
<thead>
<tr>
<th>White matter tract</th>
<th>Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Corpus callosum</td>
<td>0.72</td>
</tr>
<tr>
<td>Splenium Corpus callosum</td>
<td>0.67</td>
</tr>
<tr>
<td>Genu Corpus callosum</td>
<td>0.65</td>
</tr>
<tr>
<td>Left Cingulum (cingulate gyrus)</td>
<td>0.59</td>
</tr>
<tr>
<td>Right Cingulum (cingulated gyrus)</td>
<td>0.76</td>
</tr>
<tr>
<td>Left Superior longitudinal fasciculus</td>
<td>0.63</td>
</tr>
<tr>
<td>Right Superior longitudinal fasciculus</td>
<td>0.68</td>
</tr>
<tr>
<td>Left uncinate fasciculus</td>
<td>0.72</td>
</tr>
<tr>
<td>Right uncinate fasciculus</td>
<td>0.68</td>
</tr>
</tbody>
</table>
S8. Scree plot for general white matter factor in healthy controls

S9. Scree plot for general white matter factor in individuals with psychosis
S10. Correlations between HMOA and FA of the corpus callosum and performance on processing speed composite score and subscales in controls and individuals with psychosis

<table>
<thead>
<tr>
<th>Relationship to Cognition</th>
<th>HMOA</th>
<th>FA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOP</td>
<td>TMT</td>
</tr>
<tr>
<td>Genu – controls</td>
<td>-0.004,0.99</td>
<td>0.18,0.42</td>
</tr>
<tr>
<td>Splenium – controls</td>
<td>0.05,0.82</td>
<td>-0.02,0.92</td>
</tr>
<tr>
<td>Body – controls</td>
<td>0.12,0.60</td>
<td>0.06,0.79</td>
</tr>
<tr>
<td>Genu – psychosis</td>
<td>-0.14,0.51</td>
<td>0.13,0.56</td>
</tr>
<tr>
<td>Splenium – psychosis</td>
<td>-0.32,0.13</td>
<td>-0.25,0.24</td>
</tr>
<tr>
<td>Body - psychosis</td>
<td>-0.05,0.81</td>
<td>0.04,0.87</td>
</tr>
</tbody>
</table>

**Legend:** SOP = speed of processing composite score; TMT = trail making test; BACS-SC = brief assessment of cognition in schizophrenia – symbol coding; VF = verbal fluency; * significant correlation.
GENERAL THESIS DISCUSSION
GENERAL DISCUSSION

This thesis explored the longitudinal expression of cognitive deficits following a first psychotic episode. We further explored neuroanatomical abnormalities contributing to two cognitive domains found to have the poorest trajectory over time following illness onset. Key outputs of this thesis include identification of a poorer trajectory in verbal learning and processing speed following an initial psychotic episode, neuroanatomical anomalies in right hemisphere fronto-temporal connections associated with verbal cognitive deficits, and divergent properties of brain interconnectedness relating to processing speed deficits. This chapter will discuss the relevance of the findings in fitting with the current literature on cognition in schizophrenia, interpret their meaning, examine the strengths and limitations of the work and finally, make recommendations based on the work that may be beneficial to future research in this area.

DISCUSSION

The aim of the first paper of this thesis (Paper 1) was to investigate the course of cognitive deficit following a first psychotic episode. Consistent with the literature, global cognitive impairment is evident in individuals with psychosis at the time of their first psychotic episode and four years later. However, the majority of cognitive functioning do not deteriorate following a first episode of psychosis (FEP) in working memory, attention, reasoning & problem solving, visual learning and social cognition, suggesting that these aspects of cognitive impairment are not progressive after illness onset. In agreement, a previous thesis which in a cross-sectional manner investigated differences in the magnitude of cognitive deficit between the FEP cohort in the current thesis and a separately recruited group with chronic schizophrenia, reports that these five cognitive domains do not significantly differ between the two cohorts (Schmidt, 2010), indicating that these cognitive deficits remain stable throughout illness course. However, Schmidt (2010) reports that the trajectory of two specific aspects of cognition may be altered in comparison to the five stable domains, perhaps negatively impacted by the presence of a psychotic illness. Deficits in verbal learning were significantly greater in chronic schizophrenia cases compared to individuals at illness onset. There is also preliminary evidence for deficits of speed of processing to be more pronounced in chronic cases. These findings indicate that verbal learning and processing
speed may be susceptible to further deterioration over illness course, from onset of illness through to chronic stages of the disorder. However, due to the cross-sectional nature of the research conducted by Schmidt (2010), this conclusion can only be inferred. The current longitudinal study, intending to further elucidate the course of cognition over illness duration, reinforces the previous findings of Schmidt (2010), as verbal learning presents with a less stable course compared to other cognitive domains. In addition, speed of processing composite score reveals a less stable course at threshold levels of significance, but specifically a visual-spatial measure of processing speed (the Trail Making Test-A) and a verbal index of processing speed (verbal fluency) had a significantly poorer course over time. When those on no medication were removed from analysis, the poorer course in the processing speed composite score became significantly different from controls, possibly indicating that those on medication have a worse prognosis on this cognitive domain in the long term, however the sample size was very low in this instance (n=15). Thus, it appears the presence of an initial psychotic episode may have an impact on particular aspects of cognition over time particularly in verbal learning and processing speed. Alternatively, these abnormal cognitive trajectories over time may be the result of further neurodevelopmental deviations in individuals with psychosis throughout illness course. It is not possible to assert the exact timing of when these trajectories in verbal learning and processing speed deviate compared to the courses of the other cognitive domains. Therefore, it is possible this deviation may have developed in premorbid stages of the symptomatic onset and fall on a continuum of abnormal neurodevelopmental course beginning from emergence of cognitive deficits, usually present in early adolescence. It is worth noting that these findings are not evidence of further decline in verbal learning and processing speed subsequent to illness onset, rather the rate of change of cognitive performance is not consistent with the rate of change in healthy controls over time. In contrast, the rates of change of the five stable cognitive tasks follow a similar rate as controls. Some authors refer to this as an arrest or stagnation in cognition, where slight increases in performance in the healthy controls are not mirrored in the psychosis group (Juuhl-Langseth et al., 2014), similar to what is observed in verbal learning and processing speed in the current thesis. Additionally, it is possible that the reduced performance in verbal learning and two measures of processing speed over time may not be directly attributable to the presence of an initial psychotic episode. Other factors that typically co-occur with the onset of psychotic disorder such as social isolation, lack of employment or education may also impact adversely on neurodevelopment and these cognitive skills.
Cognitive impairments are well-established at the time of illness onset, appearing usually around early adolescence. In cases of adolescent-onset schizophrenia, a decline in verbal learning is reported over 13 years while an arrest in general cognition appears to occur (Oie et al., 2010). Therefore, it seems that the arrest of normal development in global cognition may begin in adolescents but by adulthood when psychosis emerges, around mid-to-late twenties, these deficits of cognition persist on a stable course. The only possible exceptions being verbal learning and processing speed which may persist on a poorer neurodevelopmental course up to at least four years following first-episode to an average age of 33 years, as the current thesis identifies. In general, there is a lack of longer-term longitudinal studies of cognitive changes in schizophrenia which include a well-matched control group. However, previous longitudinal studies of up to 10 years following a first psychotic episode find less stable courses in verbal learning up to ages of 38 years (Hoff et al., 2005) and also in visuo-spatial (TMT-A) and verbal measures of processing speed (verbal fluency) up to an average age of 36 years (Bergh et al., 2016), however no control group was present in the latter study. Based on these studies, it may be suggested that neuropsychological deviances in verbal learning and processing speed extend up to a timespan of late thirties.

Guided by the results of Paper 1 of the current thesis which highlights the course of verbal learning and processing speed to deviate relative to other stable cognitive domains, the subsequent two papers (Paper 2 and Paper 3) focus specifically on investigating whether structural abnormalities in the brain underlie the deficits in these cognitive domains, verbal cognition and processing speed, respectively. The arcuate fasciculus network (AF) was chosen for investigating verbal cognitive deficits in Paper 2 due to its well established role in language functions in humans (Catani et al., 2007; Lopez-Barraso et al., 2013) and the fact that lesions to the arcuate fasciculus have been linked with disorders of language such as conduction aphasia (Wernicke et al., 1874). In summary, Paper 2 reveals significant patterns of association between the AF network and cognitive function which differ between the individuals with psychosis and healthy controls. We report significant positive associations in the psychosis group between verbal learning and the microstructural organisation (FA) of the right hemisphere long AF segment as well as cortical volume of the pars opercularis in the right inferior frontal gyrus. Verbal fluency also significantly correlates with the right orbital part of the inferior frontal gyrus in this group. No significant associations between the organisation of the AF and verbal scores are present in the controls, however verbal fluency significantly correlates with lower volume and surface area of the right STG in this
group. Associations between cognitive performance and neuroanatomy that are only evident in individuals with psychosis may reflect a compensatory process, or alternatively they may reflect structural abnormalities selectively associated with functional impairment in verbal abilities in the disorder.

PET and fMRI studies show that verbal fluency tasks activate frontal regions coupled with a deactivation in bilateral STG (Schlosser et al., 1998; Frith et al., 1995) with a failure of STG deactivation suggested to occur in schizophrenia (Frith et al., 1995; Fletcher et al., 1996). The absence of an association between the STG and verbal fluency in the psychosis group is consistent with this theory of failed deactivation in the right STG, perhaps compensating by increased frontal involvement, supported by the positive relationship between verbal fluency and the right pars orbitalis in the psychosis group alone. Thus, the individuals with psychosis may engage a larger network of cortical regions in right prefrontal regions to compensate for the abnormality observed in the right STG. Further evidence of atypical pathology of the right hemisphere inferior frontal gyrus is reflected in reduced thickness in the right orbital part of the inferior frontal gyrus in individuals with psychosis and a positive association between the right long AF segment and verbal learning, a segment which projects to the right inferior frontal gyrus. Additionally, greater right laterality of the pars opercularis significantly relates to higher verbal learning scores in this group. In healthy individuals these frontal regions play a limited role in language lacking any phonological or semantic representation, with the right pars opercularis specifically activated by tonal and pseudowords (Vigneau et al., 2011). In stroke patients following left hemisphere inferior frontal gyrus infarctions, alternative cognitive strategies are developed in the form of increased right hemisphere activation. However, this compensatory mechanism has a limited effect on recovery of aphasia and may be a maladaptive reorganization of neural activation (Vigneau et al., 2011). Therefore, this role of right hemispheric frontal regions in verbal tasks in the individuals with psychosis may be maladaptive or compensatory, contributing to impairments evident in verbal performance.

Auditory verbal hallucinations (AVH) have been associated with activation of the right inferior frontal areas (Sommer et al., 2008) and to impaired connectivity in fronto-temporal language regions (Curcic-Blake et al., 2013), therefore our findings could potentially support the involvement of abnormal right hemisphere fronto-temporal regions in language function and potentially psychotic symptoms in psychosis. While in general, cognition and positive symptoms of psychosis have been shown to be relatively independent constructs,
previous studies have shown a relationship between verbal functioning and AVHs (Daalman et al., 2011; Gisselgard et al., 2014), potentially indicating that they may have some shared neural substrates. Therefore, deficits in verbal cognitive tasks and abnormalities in the brain networks involved may be potential markers of development of auditory verbal hallucinations (AVH) (Lenz et al., 2006; Klosterkotter et al., 2016). However, we did not find a relationship between verbal functioning and AVHs unlike other studies. Post-hoc, we explored a small subgroup of individuals who experienced AVHs. While we did not find an association with any individual cortical regions, our finding of an association between asymmetry of the pars opercularis and verbal learning in the psychosis group appeared to be driven by those experiencing AVHs. Sample size and consequently statistical power was low as this was not an a priori aim of the study, therefore it is recommended that future studies explicitly investigate the role of abnormal cortical asymmetry in auditory verbal hallucinations.

All significant neuroanatomical associations with verbal scores were evident in regions of the right hemisphere in Paper 2. It is possible that associations were present in the left hemisphere, particularly in the healthy controls as hypothesised, however our low sample size may not have been powered adequately to detect more subtle effects. Right hemisphere damage has been related to impaired comprehension of emotional prosody or emotional speech, comprehending and expressing emotional tone, and gesture and a sense of self (Blonder et al., 1991; Devinsky et al., 2000). Right frontal lesions have been related to impaired social awareness and behaviour (Devinsky et al., 2000). It is possible that abnormal right hemisphere fronto-temporal connectivity may be associated with other aspects of cognition and social skills and it is important that future research conducts investigations of the right hemisphere arcuate fasciculus network in relation to possible alternative explanations other than a specific language impairment.

Paper 3 particularly focuses on investigations of the neuroanatomical basis of variance in processing speed in a controls sample and related deficits in psychosis. Due to the global operational nature of processing speed, this paper examines global estimations of the brain anatomy and connectivity to investigate this cognitive skill. Initially, the novel graph theory technique was used to examine the global structural connectivity of the brain which can provide a framework for understanding cognition. While the understanding of brain structure-function mapping is still in its early stages particularly in investigations of whole brain systems (Wang et al., 2014), this paper can assist in further elucidating the biological
basis of the cognitive architecture of processing speed and related deficits in psychosis. The current paper reveals differential patterns of association between cognitive function and the global brain for healthy controls and individuals with psychosis. Initially, we report a significant association between global network topology and the processing speed composite score in the controls, not evident in individuals with psychosis. Interpretation of this association suggests that a longer average global pathlength relates to better processing speed in controls. Pathlength represents a measure of segregation of the brain, shorter pathlengths are traditionally associated with more efficient networks (Leow et al., 2013). Interpretation of these sophisticated mathematical graph theory metrics in relation to cognition and brain systems is complex and ambiguous as of yet (Ajilore et al., 2015), as a limited number of studies have directly related structural network measures to cognition. Therefore, it remains difficult to interpret how a longer pathlength or more segregated network would relate to better performance on processing speed in controls and future studies are needed to clarify this relationship.

Post-hoc investigations in Paper 3, which concentrates on the three cognitive subscales which constitute the processing speed composite score, reveal a significant association between global metrics and symbol coding scores in controls. The direction of association suggests that longer pathlengths are more conducive to better scores on this task, similarly to the composite score. No corresponding association is evident in individuals with psychosis. Similarly longer interhemispheric pathlength and corresponding lower efficiency significantly relates to symbol coding in controls, highlighting the specific role of connections which pass through the corpus callosum in processing speed tasks in psychiatric disorders, consistent with previous studies of bipolar disorder (Ajilore et al., 2015). However, regarding the Trail Making Test-A, in the psychosis group, scores relate significantly to shorter global pathlength as well as higher efficiency in temporal regions (right inferior temporal gyrus and left parahippocampal gyrus). The direction of association is opposing the associations apparent in the control group and may be indicative of differing properties of the global brain involved in the conduction of processing speed in both groups. However more research is required to determine the exact interpretation of these associations. Higher anisotropy of the genu of the corpus callosum also relates to better scores on the Trail Making Test further implicating the role of the corpus callosum in processing speed impairments. Dysconnectivity of the corpus callosum in schizophrenia is one of the most consistently findings and it is plausible this contributes to impairments on tasks of processing speed (Petterson-Yeo et al., 2011; Holleran et al., 2014). As antipsychotic medication is known to
affect motor function, it is possible that medication could have an effect on our findings with the Trial Making Test – A. However, significant findings remain after correlating for total chlorpromazine equivalents in the psychosis group. Secondary investigations of a global white matter factor of the brain reveals that a common white matter factor underlies a range of white matter tracts in controls and individuals with psychosis similar to previous reports (Penke et al., 2010; Alloza et al., 2015). This common factor suggests that the microstructural organisation of each tract is closely positively associated with organisation in all other tracts. It is suggested that pathophysiological factors that affect white matter tracts do so in a global manner rather than focused on regional tracts, thereby supporting the global disconnection theories of schizophrenia. However, we did not find an association between general white matter factor and processing speed, unlike previous studies of older adults and schizophrenia (Penke et al., 2010; Alloza et al., 2015), perhaps due to the earlier stage of illness of the participants investigated in this paper. Additionally, methodological differences between the studies may contribute to our lack of significant association with cognition, such as contrasting choice of atlas and white matter tracts included in analysis. Both Penke et al. (2010) and Alloza et al. (2015) investigated mainly general reaction time tests of processing speed with no verbal processing speed tasks, therefore global white matter may be more strongly related with simple reaction time indices of processing speed and not visuo-spatial or verbal task as employed in this paper.

In summary, this paper suggests that global brain estimates in terms of global network topology may be related to processing speed performance, particularly in the symbol coding subscale in the control group. The absence of these associations in psychosis may be indicative of pathological processes in the global network contributing to these specific processing speed deficits, however more studies are needed to confirm this. Global topology also related to the Trail Making Test subscale in the psychosis group only, with the direction of association opposite to significant associations between network topology and cognition in the control group. These opposing directions of graph network metrics involved in processing speed performance in both groups may be indicative of divergent properties of global brain properties underlying aspects of processing speed performance in both groups. This may ultimately reflect the impaired cognitive performance evident in the psychosis group. Therefore, the global operational nature of processing speed performance is reflected in these significant associations between global connectivity of the brain and cognition performance, however we failed to find associations between processing speed performance and other global brain measures investigated. More research in this area is
warranted to confirm the global nature of processing speed and if abnormalities throughout the global brain contribute to processing speed deficits in psychosis.

In integrating the results of the Paper 2 and Paper 3 of this thesis, which employ different cognitive and neuroimaging methodologies in these cohorts, evidence emerges for tentative shared abnormal neural substrates in both frontal and temporal regions and the interconnection of these regions that were associated with cognitive deficits in individuals with psychosis, (Paper 2 – right frontal-temporal cortices and interconnecting arcuate fasciculus tract; Paper 3 - temporal lobe connectivity and genu of the corpus callosum which connects the dorsolateral prefrontal cortex between the hemispheres). Abnormalities in frontal and temporal regions are one of the most consistently reported findings in adult schizophrenia studies (Thompson et al., 2001). Additionally, Paper 1 of the thesis discusses the processing speed hypothesis in psychosis and reveals that processing speed explains a large amount of variance in all cognitive tasks including verbal learning endorsing the concept of some overlap in neural substrates of these cognitive skills.

Adolescence is a time for a great deal of neuroanatomical development such as synaptic pruning (Giedd et al., 1996), with abnormal deviances in neurodevelopment potentially underlying the risk for developing psychosis. In children aged from 11-13 years at risk for psychosis, structural and functional abnormalities include regions of the right superior temporal gyrus and inferior frontal gyrus amongst other regions (Jacobson et al., 2010). Oie et al. (2010) suggest these pathological processes occurring in the developing adolescent brain may contribute to the declines or arrests in cognitive development. Longitudinal MRI studies in childhood and adolescent-onset schizophrenia show a range of abnormalities such as enlargement of lateral ventricles as well as progression of cortical grey matter loss particularly focused in parietal regions at earliest stages followed by grey matter loss in temporal and frontal regions at later stages of adolescence and early adulthood, an exaggeration of normal synaptic pruning. These abnormal processes may impede normal cognitive development throughout adolescents (Thompson et al., 2001; Gogtay et al., 2008; Rapoport et al., 1999). Similarly, using whole brain analysis techniques, reduced grey matter in a number of regions including the right superior gyrus, left medial frontal and right middle frontal gyrus, left precuneus, bilateral parahippocampal/hippocampal regions and bilateral anterior cingulate are noted in those at high risk for psychosis, which may represent neuroanatomical markers of an increased risk for psychosis (Fusar-Poli et al., 2011). In those at risk who later converted to psychosis, baseline reductions of grey matter specifically in
the superior temporal and inferior frontal cortices are associated with later transition to psychosis (Fusar-Poli et al., 2011). This tissue loss in frontal and temporal regions occurring at later stages of adolescence coincides with what has been found at first episode and chronic stages of adult-onset schizophrenia (Narr et al., 2005; Kuperberg et al., 2003; Greenstein et al., 2006). Therefore, a continuation of disturbances in the neuroanatomy of frontal and temporal regions is suggested to occur in the brains of adolescents up to adult stages of schizophrenia (Gogtay et al., 2008) with the superior temporal and inferior frontal gyri being the most predictive of conversion to psychosis (Fusar-Poli et al., 2011). Based on the findings of the current thesis which reported that the courses of verbal learning and processing speed continue on a poorer trajectory compared to other cognitive domains whose trajectory remains stable it is possible that some further neurodevelopmental deviances or mild pathological processes persist as illness progresses. These may particularly occur in brain regions and circuitries found in the frontal and temporal regions which partially underlie both verbal learning and speed of processing cognitive skills. Taken together a speculative theory may posit that specific frontal and temporal lobe abnormalities which begin to emerge in late adolescence and early adulthood schizophrenia onset may continue to interfere with cognitive functioning as illness progresses up to at least four years following symptomatic onset (at an average age of early-mid thirties as identified in the current thesis), in verbal learning and processing speed tasks specifically. Furthermore, longitudinal studies indicate the involvement of these fronto-temporal regions in psychosis onset (Smieskova et al., 2010) and preliminary longitudinal analysis in this thesis (Appendix A) shows an association between a reduction in the right hemisphere pars orbitalis (in the frontal lobe) and improved verbal learning scores over the four years in healthy controls – indicating a possible longitudinal relationship between this region and normal verbal learning functioning. The absence of this relationship in individuals with psychosis may be indicative of abnormalities in the maturation and development of this brain region following illness onset and contributing to verbal learning deficits. A significant positive association was detected between the progression of global white matter volume and processing speed scores in individuals with psychosis over the four years after illness onset that was not present in the controls. This also highlights the possibility of abnormal neuroanatomical development after a first-psychotic episode which may be associated with poorer course of cognition specifically in processing speed in this instance.
The involvement of the superior temporal and frontal gyri in the pathophysiology of schizophrenia is well established in the literature. The superior temporal gyrus encompasses important structures involved in auditory processing which are linked to language-related psychotic symptoms such as auditory hallucinations (Allen et al., 2008). Reduced volumes in the region of the inferior frontal gyrus such as the pars opercularis and pars triangularis are associated with positive symptoms of the disorder (Suga et al., 2009). Therefore, the current thesis is in line with the current literature suggesting dysfunctional fronto-temporal neuroanatomy in the pathophysiology of psychosis, specifically involved in impairments of cognition in this thesis.

It is worth identifying what, if any, impact the poorer trajectories found in verbal learning and processing speed have on functional or prognostic outcome. The current thesis found no relationship between these cognitive courses and quality of life in individuals with psychosis. Previously, certain aspects of cognition in early psychosis such as reasoning and problem solving, verbal memory and ability and processing speed are shown to relate to functional outcome (Addington et al., 1999; Allott et al., 2011). However, it is believed that psychopathological symptoms such as lifetime negative symptoms may be a stronger predictor of functional outcome as opposed to cognitive impairments (Sanchez-Torres et al., 2016). Also, the choice of measure of functional outcome in the current research, Heinrich’s Quality of Life scale, provides a global measure of functioning which is suggested to be more weakly associated with cognition (Bowie et al., 2009; Green et al., 2004). There is a strong possibility that many other predictors in addition to cognitive deficits are involved when assessing global measures of functioning such as motivation and social support (Bowie et al., 2006, 2009). Heinrich’s Quality of Life scale includes both objective and subjective measures, the latter being less associated with cognition (Tolman et al., 2010). Future studies could investigate the association of poorer course in cognition following an first-episode of psychosis and functional outcome using other scales of functioning such as performance-based measures (Assessment of Interpersonal Problem Solving; AIPPS) which are more consistently found to be associated with cognition in schizophrenia (Allott et al., 2011).

When assessing the relationship between cognitive deficits and clinical psychopathology, we report that cognition at illness onset, specifically reasoning and problem solving and social cognition scores, relate to negative symptoms four years later. Therefore, cognition at illness onset may have a predictive capacity of illness course. However, the relationship between cognitive deficits and psychopathology in schizophrenia is unclear. Some studies report
cognitive deficits, such as executive functioning to be somewhat related to negative symptoms, however the association is weak and the variance shared is often small (Donohoe et al., 2006). Other cognitive domains such as memory and attention present as being separate factors from clinical symptoms in factor analysis (Donohoe & Robertson, 2003; Donohoe et al. 2006; Lipkovich et al. 2009). While in general there is more support for a relationship between cognition and negative symptoms compared to positive symptoms (Heydebrand et al., 2004), a number of previous studies have reported an association between verbal cognitive deficits and positive symptoms of the disorder (Lencz et al., 2006; Klostrkotter et al., 2016), although this was not replicated in Paper 2. We report that neural substrates underlying verbal learning particularly in the lateralisation of frontal regions may have a role in auditory verbal hallucinations. However, sample size was low in this analysis and these results need to be interpreted with caution. If associations exist between cognitive performance and symptoms of the disorder, this further highlights the importance of studying cognition in the early stages of psychosis, particularly in premorbid stages of illness.

Strengths of the current thesis include a methodological rigorous and diverse investigation of the brain in relation to cognitive deficits in psychosis, using modern cutting-edge neuroimaging approaches including novel tract-specific measures of white matter microstructural organisation and network analysis techniques. The neuroanatomical anomalies identified using these techniques may further contribute to the biological understanding of cognitive deficits in psychosis and to the development of biomarkers of the disorder as indexed by cognitive deficits. We provide findings on the course of cognitive deficits following a first-episode of psychosis using a standardised cognitive battery designed specifically for research in schizophrenia. This will provide a coherent reference for future studies which administer the MATRICS battery to assess cognitive course in psychosis, which is the preferred consensus battery for longitudinal studies of cognition in schizophrenia (Silverstein et al., 2010).

**METHODOLOGICAL CONSIDERATIONS**

The main limitation of Paper 1 of this thesis, which investigates the longitudinal course of cognitive deficits following a first psychotic episode, was a low sample size at follow-up due to limited success in the re-recruitment of participants from the initial (baseline) time point. The attrition rate for individuals with psychosis was 38%, while the rate for controls for 65%.
General Thesis Discussion

A large proportion of individuals were un-contactable and many had relocated. A limitation in the design of Paper 2 and Paper 3, which investigates neuroanatomy in relation to cognitive deficits, is the correlational nature of parts of the analysis which limits the interpretation of those findings in terms of being able to imply in the observed associations. Paper 2 and Paper 3 report significant associations in the fractional anisotropy (FA) of white matter investigated, but not correspondingly in HMOA (although the magnitude and direction of associations using HMOA were similar to FA findings). As the response function of HMOA, which represents the diffusion signal profile of white matter fibre orientation used to estimate HMOA throughout the brain, is individually optimised, it is unclear what effect non-normalisation of the response function across individuals included, would have on our sensitivity to detect differences in the current study and investigation into this is ongoing (Leemans et al. personal communication). Diffusion MR data was only acquired at follow-up, limiting our analysis to a cross sectional design at a time point of four years subsequent to a first-episode. Therefore, we were unable to assess the neuroanatomical substrates of cognitive deficits at the time of first-episode or their alteration over time using both structural and diffusion images, which may differ from those associations identified in later stages of psychosis as reported in the current thesis.

As the majority of significant associations in connectivity metrics in Paper 3 were streamline weighted, it is worth mentioning our use of an element-wise inverse mapping during connection-to-length mapping in the generation of connectivity matrices. Due to a limited cases of extreme number of streamlines, this inversion may not be adequate in representing this range and future studies which implement more advanced inverse mappings, thresholding these extreme values, are recommended to confirm the findings in Paper 3. Other limitations of the thesis include a heterogeneous psychosis sample with a relatively benign course, making our findings potentially less generalisable to more severe cases.

Throughout the literature, linking cognitive deficits in schizophrenia to specific brain regions and circuitries have proven difficult and inconclusive. When investigating the neuroanatomical correlates of cognitive deficits in psychiatric disorders, many studies directly investigate the relationship between the neuroanatomical structure of the brain and performance scores on a range of cognitive functions similar to the current thesis. While there is no current systematic structure-function mapping for the brain, this approach is based on lesions studies which identify that particular brain regions may be related to specific cognitive functions. For example, lesions to the arcuate fasciculus have been linked with disorders of language such as conduction aphasia (Wernicke et al., 1874). However, the
clarification of how the structure of the neural connectional brain network underlies cognition and behaviour still remains one of the most critical and challenging question in neuroscience. Structural, diffusion and functional MRI investigations of the relationship between the structure of the brain and functional activation may further advance our understanding of the biological basis of cognition, as studies show that there is a close correlation between the structure of the brain and functional activity. Nonetheless, discrepancies still exist such that a relatively fixed structural organisation can produce a diverse range of functional patterns (Park and Friston, 2013) and with changes in the coupling occurring during normal development, ageing and disease. Therefore, the relationship is not simply a one-to-one mapping but intermixed with complexity. In mapping cognitive scores onto the structure of the brain in an attempt to elucidate the biological basis of cognitive deficits in psychosis, the current thesis may not have the capacity to provide direct evidence of functional relationships wherein techniques such as fMRI may have added capability. However, while this work is in its early stages, the findings of the current thesis can provide critical preliminary knowledge on the neuroanatomical correlates of cognitive deficits which future works can further probe, particularly using other imaging methodologies such as fMRI.

CONCLUSION

Cognitive ability affects everyday functioning, such as planning a dinner or remembering schedules. Deficits in cognition may adversely affect individuals with psychosis in everyday functioning, possibly even moreso than positive symptoms of the disorder. While cognitive impairments were initially believed to be core to schizophrenia in 19th century research, the emphasis was given less priority in mid-twentieth century research with a dominant focus on positive and negative symptoms of the disorder. However, in recent times the importance of studying cognition has once again returned to the attention of researchers and physicians. This thesis further strengthens the importance in studying cognitive functioning in psychosis, particularly in verbal learning and processing speed whose neurodevelopment course appears the most defective following illness onset. This thesis also highlights the importance of elucidating the underlying neurobiology of the progression of psychotic illness as indexed by cognitive deficits. Such knowledge could potentially contribute to biomarkers of the disorder which would be particularly beneficial in critical early stages of the disorder.
FUTURE DIRECTIONS

Future studies assessing cognitive deficits with longer follow-up time points following a first episode are recommended to further elucidate the course of cognitive deficits particularly of verbal learning and processing speed deficits as illness progresses. This is necessary to determine whether their trajectories continue on a negative slope and further deteriorate or whether they become stable over time. Further studies investigating the longitudinal course of the neuroanatomical abnormalities identified which relate to these cognitive deficits are also recommended, to determine how the course of these abnormalities progress. Multifaceted neuroimaging approaches incorporating functional MRI would be optimal in further exploring the neuroanatomical findings of this thesis, particularly from the time of first psychotic episode which this thesis was limited to explore.

Specific recommendations of the thesis would be to investigate the effect that non-normalisation of the response function across the sample would have on analyses which incorporate HMOA in Paper 2 and Paper 3. It is also recommended to implement more advanced inverse mappings when generating streamline weighted connectivity matrices, and further investigate the extent to which these matrices differ from those implementing more simple inverse mappings as such as in Paper 3.
REFERENCES


References


References


References


References

49. Wernicke C. (1874): Der aphäische Symptomencomplex: eine psychologische Studie auf anatomischer Basis. Cohn
Appendix A:

_Post-hoc_ investigation into longitudinal brain changes in relation to the course of cognition following a first psychotic episode

**Background**

The relationship between the change in cognition and the change in brain structures from first-episode to on average four years later was assessed. As verbal learning and processing speed had a poorer trajectory following a first-episode compared to 5 other cognitive domains assessed by the MATRICS Consensus Cognitive Battery (Attention, Reasoning & Problem Solving, Social Cognition, Visual Learning, Working Memory), we aimed to complete a _post-hoc_ examination to see if changes in neuroanatomy over time provides an indication into why these 5 areas of cognition persist with a stable deficits as opposed to verbal learning and processing speech which proceed on a poorer course over illness duration.

**Methods and Statistics**

Fifteen individuals with psychosis and 13 healthy controls were included in the longitudinal analysis. Regions chosen for this longitudinal analysis were based on the neuroanatomical findings in Paper 2 and Paper 3. Total grey and white matter volumes were chosen due to the global nature of processing speed. The parahippocampal and inferior temporal gyrus were chosen due to the significant relationship between connectivity in these regions and a visuo-spatial measure of processing speed (Trail Making Test – A). Frontal and temporal cortical regions found to be related to verbal cognition were also included (Table 1). We hypothesised that longitudinal changes in these regions may contribute to the poorer course in these specific cognitive deficits, which correspondingly will not be evident in the 5 stable cognitive deficits. FDR was applied for multiple comparisons correction in the 5 bilateral cortical regions, whereas total grey and total white matter was treated as singular investigations. Total intracranial volume was covaried for in the whole brain analysis. Age and gender were covaried for in all analysis.
**Table 1.** Brain regions included in the longitudinal analysis; CT = cortical thickness, CSA = cortical surface area, CV = cortical volume

**Results**

In the controls, a significant negative association was found between the thickness change in the right pars orbitalis over time and the change in verbal learning scores (Figure 1). In the psychosis group, the change in processing speed significantly related to the change in total white matter over time (Figure 2). No other significant associations were found which survived FDR correction (Table 3).

**Figure 1.** A reduction in the thickness of the pars orbitalis over time was significantly associated with the change in verbal learning scores in the control group.
Figure 2. An increase in total white matter over time was significantly associated with the change in processing speed scores in the psychosis group.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Psychosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing speed</td>
<td>r=0.49-0.47, p=0.055-0.96</td>
<td>r=-0.045-0.28, p=0.06-0.98</td>
</tr>
<tr>
<td>Attention/Vigilance</td>
<td>r=-0.23-0.61, p=0.01-0.98</td>
<td>r=-0.48-0.47, p=0.05-0.88</td>
</tr>
<tr>
<td>Working Memory</td>
<td>r=-0.64-0.34, p=0.26-0.91</td>
<td>r=-0.29-0.24, p=0.32-0.75</td>
</tr>
<tr>
<td>Verbal Learning</td>
<td>r=-0.60-0.55, p=0.13-0.93</td>
<td>r=-0.42-0.49, p=0.04-0.98</td>
</tr>
<tr>
<td>Visual Learning</td>
<td>r=-0.52-0.38, p=0.04-0.99</td>
<td>r=-0.38-0.45, p=0.06-0.94</td>
</tr>
<tr>
<td>Reasoning &amp; Problem Solving</td>
<td>r=-0.30-0.34, p=0.20-0.99</td>
<td>r=-0.43-0.49, p=0.039-0.98</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>r=-0.46-0.54, p=0.032-0.98</td>
<td>r=-0.43-0.48, p=0.045-0.93</td>
</tr>
</tbody>
</table>

Table 3. Negative findings between cognitive tests and brain regions investigated (r and p ranges reported).
Discussion

A reduction in the thickness of the pars orbitalis over time was significantly associated with the change in verbal learning scores in the control group and this may be representative of synaptic pruning in this area which is known to occur in language regions and is involved in specialisation of languages (Sowell et al., 2004). Correspondingly this synaptic pruning may not occur in individuals with psychosis resulting in poorer trajectory in verbal cognition. Additionally, an increase in total white matter related to processing speed in the psychosis, which was not evident in the controls may also be indicative of a pathological process. As no other longitudinal changes in brain regions significantly related to the 5 cognitive domains with stable deficit, it may indicate that these neuroanatomical progressions relating to poorer verbal learning and processing speed course after illness onset, may not adversely affect these cognitive domains. Sample size was low in this post-hoc analysis and only a limited number of regions were investigated, therefore future research is needed to confirm these findings.