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Anatomical Correlates of Working Memory Deficits in Schizophrenia

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Résumé

La mémoire de travail — c'est-à-dire la capacité limitée de retenir et de manipuler temporairement l'information — est un déficit cognitif central en schizophrénie. La perturbation de cette fonction possède un fort impact dans la vie quotidienne des patients. Des travaux récents de notre laboratoire ont pu mettre en évidence que ces troubles de mémoire de travail ne sont pas homogènes et que certains processus sont plus perturbés que d'autres. Par exemple, une méta-analyse du laboratoire a démontré que l'encodage volontaire d'information est une des fonctions spécifiquement affectée en schizophrénie (Grot, Potvin et al. 2014). Plus spécifiquement, l'association volontaire d'informations distinctes en un ensemble cohérent (par exemple, un objet et sa position spatiale) est déficitaire chez les patients. Ce déficit spécifique est notamment sous-tendu par une hypoactivation du cortex préfrontal et pariétal chez les patients (Grot, Légaré et al. 2017). Ces deux régions sont liées à l'attention, à la manipulation d'information, et aux stratégies d'encodage, ce qui confère l'habilité et la flexibilité nécessaire à la mémoire de travail (Kane and Engle 2002, Baddeley 2003). Il est intéressant de noter que de nombreuses études rapportent aussi une réduction de l'épaisseur corticale de ces régions chez les patients, ainsi qu'une altération des fibres blanches les interconnectant (Goldman, Pezawas et al. 2009). En ce sens, notre étude a montré qu'une modification anatomique du réseau préfrontal-pariétal pourrait expliquer le déficit spécifique de mémoire de travail en schizophrénie. Plus spécifiquement, la latéralisation gauche de ce réseau serait atténuée en schizophrénie, et engendrerait le déficit observé en mémoire de travail.

Mots-clés: Schizophrénie, Mémoire de Travail, Imagerie de Diffusion, Épaisseur Corticale

Abstract

Working memory, which is the limited capacity to temporarily maintain and manipulate information, is a core cognitive deficit in schizophrenia. This impairment has a strong impact on the daily lives of patients. A previous study of our laboratory observed that working memory deficits are not homogeneous and that some processes are more disturbed than others (Grot, Potvin et al., 2014). This was supported by a subsequent study, which showed that the voluntary association of distinct information into a coherent whole (i.e. an object and its spatial position) was specifically impaired in patients with schizophrenia (Grot, Légaré et al., 2017). This specific deficit, which is referred to as active binding, is underpinned by a hypoactivation of the left prefrontal and parietal cortex in patients (Grot, Légaré et al., 2017). These two regions are related to attentional processes, manipulation, and encoding strategies, which confer the skills and flexibility required for working memory (Kane and Engle 2002, Baddeley 2003). Interestingly, numerous studies report a cortical thickness reduction in these regions, as well as an alteration of the white fibres interconnecting them in patients with schizophrenia (Goldman, Pezawas et al., 2009). Accordingly, our study showed that anatomical modifications of this network could underpin the specific active binding deficit observed in schizophrenia patients. More specifically, a reduced leftward lateralization of the prefrontal-parietal network could contribute to this specific working memory deficit in patients.

Keywords: Schizophrenia, Working Memory, Diffusion Imaging, Cortical Thickness

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Abbreviations

ACC: Anterior Cingulate Cortex

AF: Arcuate Fasciculus

ANOVA: Analysis of Variance

BrA: Brodmann Area

Ba: Active Binding

Bp: Passive Binding

CSF: Cerebrospinal Fluid

CVLT: California Verbal Learning Test

DLPFC: Dorsolateral Prefrontal Cortex

DMN: Default Mode Network

DSM: Diagnostic and Statistical Manual of Mental Disorders

DTI: Diffusion Tensor Imaging

DWI: Diffusion Weighted Imaging

EP: Echo Planar

FA: Fractional Anisotropy

FAL: False Alarm

FDR: False Discovery Rate

FMRI: Functional Magnetic Resonance Imaging

GM: Gray Matter

IQ: Intelligence Quotient

IUSMM: Institut Universitaire en Santé Mentale de Montréal

LI: Laterality Index

LTM: Long Term Memory

MATRICS:

MGF: Middle Frontal Gyrus

MNI: Montreal Neurological Institute

MRI: Magnetic Resonance Imaging

NK: Newman-Keuls

PANSS: Positive and Negative Syndrome Scale

PFC: Prefrontal Cortex

QC: Quality Control

RFT: Random Field Theory

ROFC: Rey–Osterrieth Complex Figure Test

ROI: Region of Interest

Sec: Seconds

SCID: Structured Clinical Interview for DSM Disorder

SLF: Superior Longitudinal Fasciculus

STM: Short Term Memory

UF: Uncinate Fasciculus

UNF: Unité de Neuroimagerie Fonctionnelle

UFOV: Useful Field of View

VLPFC: Ventrolateral Prefrontal Cortex

WAIS: Weschler Adult Intelligence Scale

WCST: Wisconsin Card Sorting Test

WM: White Matter

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Introduction

1. Schizophrenia

a) General

Schizophrenia is a chronic disease which alters the behaviour, thoughts, and general functioning of affected individuals (National Institute of Mental Health 2015). It is characterized by three main symptoms categories: positive, negative, and cognitive. Positive symptoms include psychotic manifestations such as hallucinations, delusions, and thought disorders (National Institute of Mental Health 2015). Negative symptoms refer to a diminution of normal functions, such as depression, reduced emotional expression, and lower general pleasure (National Institute of Mental Health 2015). Finally, cognitive symptoms include reduced attentional capacities, inability to understand and use information in order to attain a goal, and lower learning capacities (National Institute of Mental Health 2015). Those symptoms create a general lower quality of life, and the impacts on patients, but also on society are broad. The main characteristics and consequences of this devastating disease will be described below.

Prevalence, Impact on Society and Patients

Schizophrenia affects about 1% of the Canadian population (Health Canada 2002), and about 21 million people worldwide (World Health Organization 2017). This percentage rises to 8-12% for individuals having a schizophrenic sibling or parent, and to 40-50% for identical twins (Tamminga and Holcomb 2004). Men and women are equally impacted, although men usually develop the symptoms approximately 5 to 7 years earlier (Health Canada 2002, Tandon, Nasrallah et al. 2009). Moreover, women usually present fewer cognitive impairments, fewer negative symptoms, better social functioning, typically respond better to treatment, and have a generally better global outcome (Grossman, Harrow et al. 2008, Luoma, Hakko et al. 2008, Tandon, Nasrallah et al. 2009, APA 2013).

Impact on Patients

The impact of this disease on a patient life is profound. Patients have a reduced ability to maintain a number of facets of their lives, such as social interactions, employment, self-care, as well as having a generally reduced quality of life (Health Canada 2002, Canadian Psychiatric Association 2005, Carpenter 2008). Schizophrenia arises in early adulthood, with an onset between 15 and 45 years (Tandon, Nasrallah et al. 2009). The age of onset is related to the severity of symptoms. Indeed, patients diagnosed before the age of 20 present more negative and cognitive symptoms, and usually have a worse prognosis (Tohka, Zijdenbos et al. 2004, Luoma, Hakko et al. 2008). Moreover, about 52% of the patients hospitalized are aged between 25 and 44 years old (Health Canada 2002). This early onset often refrains patients from forming families, creating social ties, maintaining employment, or completing their education (Health Canada 2002). In fact, 60 to 70% percent of patients do not marry, and many withdraw from social circles during the early years of the illness (Health Canada 2002).

Patients also have a reduced life expectancy (Canadian Psychiatric Association 2005). When untreated, their lifespan is shortened by roughly 15 to 20 years (Tandon, Nasrallah et al. 2009). This is due to a number of factors such as comorbid mental disorders including anxiety, depression, and intellectual disability (Ciapparelli, Paggini et al. 2007, Tandon, Nasrallah et al. 2009). Mental disorders also increase death by suicide. Indeed, suicide is higher in patients than in the general population, a phenomenon linked to comorbid depression, substance abuse, medication discontinuation, and increased impulsivity (Tandon, Nasrallah et al. 2009). This results in a 40 to 60% increase in suicide attempts, leading to a 10 to 15 times increased likelihood of death by suicide in schizophrenic patients compared to the average population (Elizabeth D. Radomsky, Gretchen L. Haas et al. 1999, Health Canada 2002). Furthermore, comorbid physical disorders also reduce lifespan, and include increased cardiovascular incidence, diabetes, metabolic syndrome, and pulmonary disease (APA 2013). Schizophrenic patients usually have an increased risk of physical disorders, due to increased obesity, cigarette smoking, sedentary life, as well as a reduction of access and quality of care (Tandon, Nasrallah et al. 2009, APA 2013). Lastly, prognosis is generally more favourable when a number of factors are present such as superior premorbid phase, greater neurocognitive capacity,

female gender, lack of substance use, and late onset (Flyckt 2006, Tandon, Nasrallah et al. 2009).

Impact on Society

Although representing a small proportion of the population, schizophrenia creates a high burden on the society, the health care system, as well as on the families. In 1996, the direct cost of schizophrenia in Canada was about 2.35 billion $ (Health Canada 2002, Goeree, Farahati et al. 2005). This is due to hospitalization, assistance plans, incarceration costs, comorbidity, as well as reduced employment (Health Canada 2002). Indeed, the patient population is over-represented in incarceration and homelessness situations, with about only 1/5 of patients having a full-time job (Health Canada 2002, Robert Rosenheck, Douglas Leslie et al. 2006, Tandon, Nasrallah et al. 2009). A 2002 review of literature reported that on average, 11 % of homeless people suffer from schizophrenia (Folsom and Jeste 2002). As for incarceration, a longitudinal study showed that about 9% of patients will be incarcerated four years after the disease onset (Jonathan D. Prince , Ayse Akincigil et al. 2007). Finally, a proportion of patients as high as 80% will have episodes of substance abuse (Health Canada 2002). This increases suicidal thoughts, violence, incarceration rate, and reduces recovery (Munetz, Grande et al. 2001, Tandon, Nasrallah et al. 2009).

Importantly, about half of the patient population worldwide does not receive care, and if they do, it is mostly at the community and family level (World Health Organization 2017). Families of patients show higher subjective and objective burden than any other chronic disease (Magliano, Fiorillo et al. 2005, Tandon, Nasrallah et al. 2009). Moreover, they usually have lower social and professional support in comparison to families of patients with other chronic diseases (Magliano, Fiorillo et al. 2005, Tandon, Nasrallah et al. 2009). Finally, stigmatization leads to discrimination, fear, reduced self-esteem, which can precipitate social withdrawal (Read, Haslam et al. 2006).

All in all, schizophrenia is a debilitating disease, which has a great impact not only on patients, but also on their family, and society in general. The combination of symptoms, which have their onset very early in life, as well as the prejudice accompanying this disease, prevents a decent quality of life, and creates social isolation.

Patients are overrepresented in incarceration and in homelessness situations, and often have substance abuse problems, which create a number of other consequences such as violence, and suicide. Schizophrenia research is therefore crucial, in order to better understand its aetiology and pathophysiology, and support patients suffering from this devastating disease.

b) History

The progression of the inclusion criteria of schizophrenia not only affected diagnosis, but research as well, as its evolution led the way in the development of pharmacotherapies. It is critical to assess the progression of the inclusion criteria in order to understand the current knowledge of this disease. Schizophrenia is a highly heterogeneous disease, and the diagnostic weight put on individual symptoms created a bias towards psychotic symptoms. In fact, research has not only been delayed due to the complex nature of the disease, but also because of the lack of consensus in the identification, and core nature of the disease (Carpenter 2008).

Kraeplin, Bleuler and Scheinder

In the late nineteenth century, Emil Kraepelin described a large cluster of diseases sharing a common pattern, which he named "dementia praecox", literally meaning "cognitive decline with onset in youth" (Hoenig 1983, Tandon, Nasrallah et al. 2009, Jablensky 2010). Manifestations of the disease all lead to cognitive and behavioural decline, and seemed to follow the same temporal course, such as similar type and time of onset (Carpenter 2008). What he called "dementia praecox" included diseases like paranoia, catatonia, and thought disorder.

Later, Bleuler (1911) coined the term "schizophrenia", literally split mind, insisting on the fact that "the split of several psychic functions is one of its most important characteristic" (Bleuler 1951, Hoenig 1983). Split mind highlighted the hypothesis that patients had a mental rupture within thought, affect and behaviour (Carpenter 2008). It also permitted the use of the plural form "schizophrenias", as Bleuler insisted that schizophrenia was not a disease by itself, but rather a group of diseases (Tandon, Nasrallah et al. 2009). Bleuler also divided the symptoms into two categories, basic and accessory (Jablensky 2010). The basic, fundamental symptoms, which he

believed were present in all cases, included thought disorder, discordant affect, loosening of associations, autism, and withdrawal from reality (Fonov, Evans et al. 2009, Jablensky 2010). On the other hand, the accessory symptoms resembled what is now called positive symptoms, such as hallucinations, and delusions (Jablensky 2010).

The symptom balance changed dramatically in the mid-twentieth century, due to the increasing need for a reliable, specific diagnosis. Psychotic symptoms being more easily characterized were thus put in the forefront of the diagnostic criteria. Schneider proposed that nine groups of psychotic symptoms be of crucial weight in the diagnosis; such as delusions, out of body experience, and voices (Schneider 1950, Jablensky 2010). Those "first rank symptoms" were included in the DSM-III with the hopes of increasing the diagnosis accuracy, thereby renouncing to the central cognitive deficit present in Kraeplin and Bleuler's schizophrenia model, and establishing reality distortion as the major manifestation of this disease. From this point, most clinical trial measured antipsychotics therapeutic response through psychosis, while cognitive and negative symptoms were mostly left out (Carpenter 2008). In fact, the psychosis treatment efficacy was considered as efficacy to treat the whole schizophrenia spectrum (Carpenter Jr 2004). Still, a number of studies showed that those psychotic symptoms do not accurately predict the patient outcome (Michael Foster 1996, Waters 2009). In fact, psychotic symptoms were shown to be the worst predictors of functional outcomes of all three symptom categories (Michael Foster 1996). On the other hand, certain neurocognitive measures, such as the Wisconsin sorting card task (WSCT), were more predictive of functional outcome than psychotic symptoms (Michael Foster 1996).

Finally, in an attempt to characterize schizophrenia more accurately, Strauss (1974) introduced the tripartite model in 1974 (Carpenter Jr 2004). This concept was proposed to address the issue of the low association between various clinical symptoms. The separation of psychotic positive, negative, and cognitive symptoms permitted the etiologic study and treatment of each symptom category. Supporting this, Carpenter Jr (2004) found that while there was low within-subject correlation between the three symptom categories, each symptom category had a highly predictive power within itself for each individual. This therefore put back on the forefront the hypothesis that

schizophrenia is a group of diseases, emphasizing the importance of its study through various collection of symptoms (Carpenter Jr 2004).

All in all, there was an important evolution of the definition of schizophrenia, as this disease seems to differ between individual regarding the extent of the expression of each symptom category. Taking all those factors into account, the current diagnosis criteria of schizophrenia will be exposed below.

c) Diagnosis of Schizophrenia

The diagnosis for schizophrenia is still broad, and mostly based on subjective measures (Jablensky 2010). The diagnosis criteria, as defined by the *Diagnostic and Statistical Manual of Mental Disorders V* (DSM-V, 2013), are as follows[1]:

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.

2. Hallucinations.

3. Disorganized speech (e.g., frequent derailment or incoherence).

4. Grossly disorganized or catatonic behaviour.

5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the

[1] Definition taken verbatim from the DSM-V, 2013

onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Diagnosis can also be made with specifiers such as the number of episodes (first episode, or multiple episodes), the current period (acute, remission, partial remission, or continuous), the severity of symptoms, or if the illness is accompanied by catatonia (APA 2013)

Following this definition it is clear that the diagnosis is still highly skewed towards psychotic symptoms, as hallucinations, disorganized speech or delusion must be present for at least one month in order to be diagnosed. This represents the Schneiderian point of view that schizophrenia is mainly a psychotic illness. Negative symptoms are part of the diagnosis, however, not crucial. The chronic aspect of the disease is also present, as impairment in various functions has to be present for at least 6 months (Criterion C). Interestingly, cognitive symptoms are not part of the core diagnosis. The addition of those symptoms to the DSM-V was considered, but they were excluded in the end. Indeed, some argued that cognitive symptoms were not adequate for differential diagnosis, as they are present in a number of other psychotic disorders (Barch, Bustillo et al. 2013). For example, the neurocognitive profile of bipolar and schizophrenic patients is quite similar for verbal memory and speed processing (Barch, Bustillo et al. 2013).Yet, the progression of cognitive impairments can usually distinguish between those two disorders. Indeed, schizophrenia is characterized by cognitive impairments present before the onset, which will stay stable throughout the disease. On the other hand, bipolar individuals present increased cognitive dysfunction during active phases, such as mania or depression (Barch, Bustillo et al. 2013). Nonetheless, cognitive symptoms still have a strong influence on Criterion B, which is the impairment of functioning in one or more aspect of life (APA 2013). Moreover, the cognitive decline present before the onset of the disease could also be important for early diagnosis, as described below.

d) Evolution of Disease

Schizophrenia develops over time, and can be divided into a number of periods. Yet, it is important to note that those phases are not always clearly demarked (Tandon, Nasrallah et al. 2009). During childhood, individuals who will later develop the disease have a number of subtle cognitive, motor and social impairments (Tandon, Nasrallah et al. 2009). This constitutes the premorbid phase, which includes attention deficits, poor social interactions, and late motor developments (Tandon, Nasrallah et al. 2009). The prodromal phase occurs before the first full-scale psychosis, and is characterized by cognitive and negative symptoms (Tandon, Nasrallah et al. 2009). This phase can last

from months to years, with 5 years as the mean (APA 2013). Attenuated positive symptoms, such as subthreshold hallucinations or delusions, also transpire up to one year before the first episode psychosis hospitalization (Tandon, Nasrallah et al. 2009). Individuals can show eccentric beliefs, perceptions, disorganized speech and behaviour, as well as social withdrawal (APA 2013). As stated, this phase is part of the diagnosis criteria, and must occur for at least 6 months before onset (Criterion C) (APA 2013). Illness onset is defined by the diagnostic criteria of the DSM-V, and therefore individuals must present their first "full-blown" psychotic episode (Tandon, Nasrallah et al. 2009, APA 2013). After the first psychotic episode, the course of the disease is usually made up of episodes of recovery intertwined with relapsing psychotic breaks, with greater functional deterioration during the first five years (Tandon, Nasrallah et al. 2009). The symptoms then stabilize, as the positive symptoms usually attenuate with years, a phenomenon thought be related to the decline in dopamine with age (Tandon, Nasrallah et al. 2009, APA 2013). On the other hand, negative symptoms usually increase (Tandon, Nasrallah et al. 2009, APA 2013). As for cognitive symptoms, they stay stable, or show low improvement over the course of the illness (Tandon, Nasrallah et al. 2009, APA 2013, Keefe 2014). Thus, cognition is not only impaired before psychosis, but those deficits are also stable throughout life, a pattern typical of schizophrenia (Barch, Bustillo et al. 2013) The absence of improvement of those functions is an important obstacle for recovery (APA 2013).

Taken together, the three principal symptoms of schizophrenia are regarded in a very different way, and their individual importance evolved throughout history. Positive symptoms have the greatest diagnosis weight, and are the principal target of pharmacotherapy (Carpenter Jr 2004, Tandon, Nasrallah et al. 2010). Yet, those symptoms usually become less prominent during illness progression. Negative symptoms are presently not treated by medication, and usually persist or worsen (Carpenter 2008). Finally, cognitive symptoms are present before onset, and have a relative stability throughout the disease. This could be not only important for early diagnosis, but for the study of cognitive symptoms as endophenotypes. In fact, cognitive symptoms are present in first-degree relatives, who generally show intermediate values, suggesting that there could be a genetic contribution, and that cognitive symptoms could be a cause, and not a

consequence of the disease (Tamminga and Holcomb 2004, Braff 2015). This could be advantageous, as the study of first-degree relatives could eliminate many variable such as chronic medication, institutionalization and psychosis (Cornblatt 1994). Moreover, given the high heterogeneity of the disease, it would be advantageous to study more quantifiable values, such as performance in certain cognitive tasks, than the subjective characteristics of positive and negative symptoms (Tamminga and Holcomb 2004). Cognitive symptoms are the greatest impediment to quality of life and recovery, social life and work, and predict a worst prognosis (Michael Foster 1996). Furthering our understanding of cognitive impairment in schizophrenia could not only increase the quality of life of the patients, but also improve the understanding of the basic underlying deficits of schizophrenia.

2. Cognitive Symptoms of Schizophrenia

Cognitive deficits are a core symptom in schizophrenia, and more than 80% of patients have a deficit in at least one measure (Toulopoulouand and Murray 2004, Jablensky 2010). In average, patients will be between half to one and a half standard deviation below the general population for a number of cognitive measures (Heinrichs and Zakzanis 1998, Cirillo and Seidman 2003). The remaining of the population is considered as "high functioning", as they show similar performance as healthy controls on several cognitive tests. Yet, they are still considered below normal range (Hoff , Palmer, Heaton et al. 1997, Toulopoulouand and Murray 2004). For instance, it was suggested that the 20% of patients scoring in the normal range had higher than normal functioning before onset (Wilk, Gold et al. 2005). This was supported by a study which observed that when matched by Intelligence Quotient (IQ), patients performed below controls in a number for neuropsychological tests (Wilk, Gold et al. 2005). Following this logic, "high-functioning" patients would have a deficit compared to their pre-onset values, but would fall into the general population values after onset. Nonetheless, it is important to mention that most patients have a lower IQ than the average population (Bowie and Harvey 2006). This is observed during the premorbid phase, and it seems to decline with onset (Bowie and Harvey 2006). Moreover, as for high-functioning patients, patient with low IQ will still show cognitive deficits even when matched by IQ to healthy

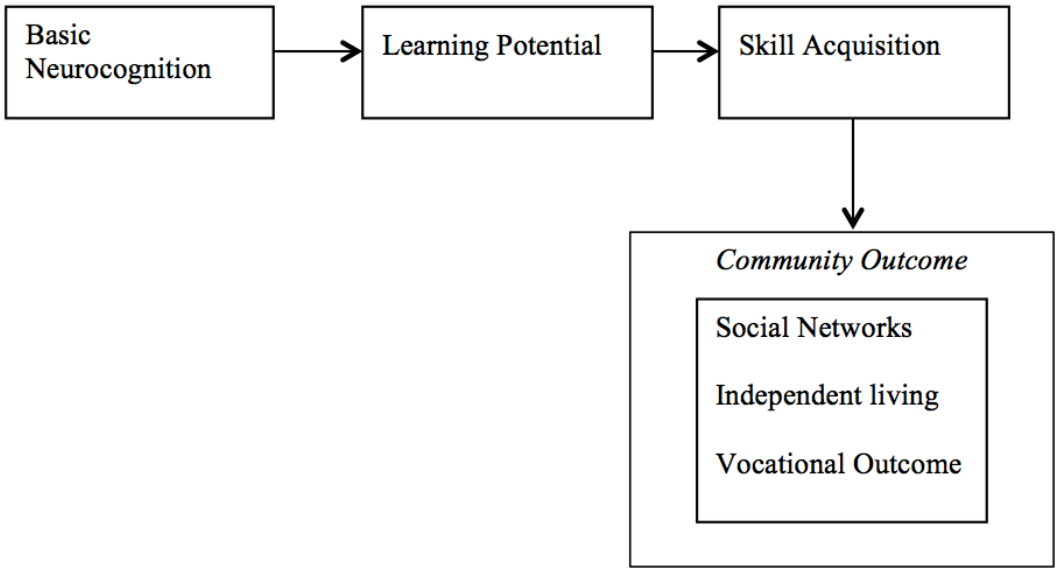
controls (Kremen, Seidman et al. 2001, Bowie and Harvey 2006). Therefore, cognitive deficits are not a result of a lower general intelligence.

As pointed out in the previous section, cognitive deficits appear before onset, are not a consequence of the illness, and will persist in a relatively stable manner during the illness (Jablensky 2010). During the premorbid phase, cognitive deficits have an average effect size of 0.5 (Tandon, Nasrallah et al. 2009, Trotta 2015). Before or at the time of onset, cognitive impairment usually increases, after which there is generally a mild improvement or stability. Still, the cognitive performance of patients is usually lower than controls throughout the illness, and occasionally declines with the disorder's duration (Kremen, Vinogradov et al. 2010). Moreover, antipsychotic medication as no to little effect on cognitive symptoms (Keefe, Bilder et al. 2007). Generally, second generation atypical antipsychotics are more effective than first generation medication, but the effects on cognitive symptoms are still low (Keefe, Silva et al. 1999). Supporting this, a meta-analysis including 15 studies using atypical antipsychotics showed that verbal fluency and executive function are some of the most improved functions, with attention responding to a lesser extent, and learning and memory being the least affected by medication (Keefe, Silva et al. 1999). Yet, a more recent meta-analysis suggested that first-generation antipsychotics are not totally ineffective (Mishara and Goldberg 2004). Indeed, it was found that they have modest to moderate effects sizes on a number of cognitive symptoms such as automatic and perceptual processing, attention, memory and language, and executive function (Mishara and Goldberg 2004). Nonetheless, most studies agree that pharmacological improvements of cognitive symptoms are still very low, even if some beneficial effects are observed.

Cognitive symptoms are also present as an intermediate phenotype in relatives (Toulopoulou, Picchioni et al. 2007, Tandon, Nasrallah et al. 2009), and are greatly related to functional outcome (Michael Foster 1996, Green, Kern et al. 2004, Carpenter 2008). Indeed, Green's influential reviews proposed that global outcome would be related to cognitive deficits (Green 1996, Green, Kern et al. 2004). Deficits such as episodic memory, working memory, vigilance, and executive functioning, have the greatest correlation to functional outcome (Green, Kern et al. 2004). Indeed, Green (1996) argues that learning potential is correlated with everyday quality of life, as it permits the

acquisition of new skills, which could contribute to a number of crucial aspects in life (Figure 1).

Figure 1: Figure Adapted from Green (2000); Learning Potential is Related to Everyday Quality of Life



The importance of cognitive symptoms on global outcome led to a tremendous increase in the cognitive deficit research in schizophrenia, which resulted in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. This conference established seven categories of core cognitive deficits, such as speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition (Nuechterlein, Barch et al. 2004, McClure, Romero et al. 2007). Yet, not all functions are affected the same way in every patient. A meta-analysis by Fioravanti et al. (2005) showed that although there was a global reduced cognitive function in patients with schizophrenia compared to healthy control, there was a high heterogeneity in the degree to which each process is affected. This finding was re-established seven years later, illustrating the stability of the finding (Fioravanti, Bianchi et al. 2012). As there is a high heterogeneity of symptoms, this review will concentrate on a few cognitive deficits,

which are considered to be the most consistently affected in patients (Cirillo and Seidman 2003).

a) Attention

Attention is crucial, as it provides a filter for the great amount of information perceived in everyday life. Inputs compete for priority, and attention can create a bias towards certain information (Braff 1993, Daniel H. Mathalon, Theda Heinks et al. 2004, Luck and Gold 2008). Attention is thus an essential process as it regulates perception, memory, and response selection, thereby influencing a number of other cognitive processes, such as working memory and executive control (Luck and Gold 2008). Impaired attention in schizophrenic patients has been highly documented, and is now considered a fundamental deficit (Fioravanti, Carlone et al. 2005, Fioravanti, Bianchi et al. 2012). The deficits in attention are present before onset, and are shared with first-degree relatives, suggesting a genetic contribution (Bowie and Harvey 2006). Although the definition of attention seems quite straightforward, this function is multifaceted, and modulated by a number of factors (Carter, Bizzell et al. 2010). The various types of attention will be described below.

Sustained attention. First, attention can be transient or sustained. Sustained attention is the ability to focus continuously, without being distracted, for the period of time necessary to complete a task. For example, it is required when reading a book, as individuals with impaired sustained attention would constantly be distracted and unable to finish a page. On the other hand, transient attention is the ability to increase attention at a moment when a task is more demanding. Therefore, while sustained attention is needed throughout a task, transient attention is required at specific moments that are important for the task's performance (Bozikas, Andreou et al. 2005, Fioravanti, Carlone et al. 2005, Carter, Bizzell et al. 2010). When performing a task, patients with schizophrenia will show a greater decline in sustained attention with time compared to controls, suggesting that they are unable to maintain a constant attentional level (Hahn, Robinson et al. 2012). This decline increases with task difficultly and cognitive demand (Hahn, Robinson et al. 2012). However, even at the beginning of the task, attentional levels are lower in patients, suggesting that the sustained attention would not be responsible for the whole deficit (Hahn, Robinson et al. 2012). Carter, Bizzell et al. (2010) designed a mix block/event-

related task that allowed the separation transient and sustained attention. The overall performance in patients was reduced compared to controls, and altered activations were reported for both types of attention. Indeed, Carter et al. (2010) found that although the attentional network regions, which will be described in more details below, were more active during sustained attention, they presented a lower activation during the transient attention compared to controls (Carter, Bizzell et al. 2010). The authors hypothesized that this was due to an irrelevant control of attention. Indeed, while healthy controls increased their attention network during relevant stages, patients were unable to effectively control their attention, resulting in a hypoactivation during transient attention compared to controls. In short, patients might recruit the attentional network to a greater extent during less demanding tasks, until task demands would become too high, at a point which their activation would be unable to compensate (Karch, Leicht et al. 2009, Carter, Bizzell et al. 2010). This would therefore imply inefficient activation in patients (Karch, Leicht et al. 2009, Carter, Bizzell et al. 2010). Hence, patients are unable to maintain attentional levels during an extended period, representing impaired sustained attention. Furthermore, they are unable to increase their attention at critical moments, representing dysfunctional transient attention.

Selective attention. Selective attention is the capacity to choose and enhance the information processing of relevant information, while decreasing irrelevant information in order to attain a goal (Braff 1993, Cameron S. Carter, Mark Mintun et al. 1997). For example, in a big crowd, it would be necessary to focus on the speech of the person talking to us, while ignoring other conversations and sounds. Therefore, selective attention requires voluntary processing, and this function is impaired in patients (Fioravanti, Carlone et al. 2005). Indeed, patients have trouble focusing their attention on low valence cues (Braff 1993). On the other hand, involuntary attention is linked to the valence one attributes to a stimulus (Braff 1993). This type of attention is performed in a passive way, as the stimuli which are attributed a high valence will be processed in high priority. For instance, when the desired input has a high valence, its processing would require less control of attention. This type of attention seems to be spared in patients (Braff 1993). Supporting this, the importance of selective attention can be highlighted when the target used for goal directed behaviour is not the most salient (Braff 1993, Luck

and Gold 2008). This was illustrated in a study by Hahn, Robinson et al. (2010), which tested the effect of salience on selective attention in schizophrenia. During a visuospatial task, half of the target stimuli flickered, thereby increasing their salience, while the other half did not flicker. Increased target salience benefited both controls and schizophrenic patients. However, when the target had low salience (non-flickering target), controls preferentially remembered the non-flickering target, while patients preferably remembered the flickering stimuli. Thus, patients had trouble overcoming salient cues, supporting the hypothesis that patients have trouble in selective attention, and this especially when the target has low salience.

When discussing selective attention, an additional distinction was pointed out by Luck and Gold (2008). In fact, selective attention could be characterized by rule selection and input selection. Rule selection can be exemplified by the Stroop task, which usually consists of coloured words (e.g. the written word "Green" coloured in blue). In this task, participants are told to either read the words (here, "Green"), or state the colour of the word (here, "blue"). Rule selection is the process by which participants have to choose between competing rules, such as the "read the word" or "say the colour". Therefore, rule selection is the ability to apply a rule to a task. On the other hand, input selection is the ability to choose an input, and is further characterized by the control of selection, and the implementation of selection. The control of selection is the process by which one determines which input needs to be selected, while the implementation of selection is the process by which one reduces irrelevant inputs and enhances relevant inputs. The authors argue that schizophrenic patients have trouble in the control of selection, but not in the implementation of selection. Indeed, patients usually are able to perform in spatial cueing paradigms, which requires individuals to enhance the processing of the cued location, and therefore suggests an intact implementation of selection in schizophrenia (Luck and Gold 2008). On the other hand, when patients are informed that the target will appear on the opposite side of the cued location, patients present a low performance. This involves controlling the selection, and overriding the prepotent rule of enhancing the cued location. Hence, patients have a deficit in the control of selection, directing their attention to the right target, especially when the input has low salience and requires top-down attention, or when the appropriate rule is not the default one. Top-down control is the

ability to control perception with cognition, while bottom-up control is the process by which perception controls cognition. For example, when the target stimulus is the most salient, bottom-up control will suffice, as that stimulus will be processed in priority. On the other hand, when the target stimulus is not the most salient, top-down control is crucial in order to select the appropriate information. Therefore, patients with schizophrenia are deficient in rule selection and input selection task, but only when the latter necessitates a high level of control of selection, and top-down control. The control of selection happens in the prefrontal and parietal cortex, while the implementation happens in the cortex of the input's modality (Luck and Gold 2008). Therefore, patients would have a specific selective attention deficit, due to the fact that they are unable to accurately select the target or rule when they are in competition.

Divided attention. Divided attention is the ability to attend to multiple inputs at once, and thus "splitting" attentional resources to multiple targets. This can be illustrated by talking on the phone while writing. Indeed, in order to succeed, one needs to listen to the individual, as well as concentrate on writing the appropriate information. Patients have a deficit in broad attention, i.e. when one has to attend a high number of inputs (Hahn, Robinson et al. 2012). Indeed, Hahn and colleagues (2012) used a visuospatial attention task, in which either one, two or four possible target would be cued. The target then appeared in either one of the cued locations (valid trial), or in a non-cued location (invalid trial). They found that patients had a greater deficit when presented with four cues than in invalid trials. The authors conclude that patients have a deficit when a task requires broad monitoring (Hahn, Robinson et al. 2012). On the other hand, Gray, Hahn et al. (2014) performed a Useful Field of View (UFOV), in which it is possible measure the ability of individuals to divide their attention between peripheral and central locations. Participants had to identify the target that had been presented in both those locations, and a significant deficit in the divided attention was seen in patients compared to controls (Gray, Hahn et al. 2014) The authors concluded that this divided attention deficit could be due to either the inability to handle two stimuli at the same time, the inability monitor the environment in a broad way, or due to the fact that patients tend to give one location greater weight, resulting in hyperfocusing (Gray, Hahn et al. 2014) Following this, a recent study tested the hyperfocusing hypothesis, performing a test in

which individuals were asked to either focus on the central, or peripheral area (Kreither, Lopez-Calderon et al. 2017). Patients showed an increased processing of the central element, and increased inhibiting of peripheral information, but they failed to inhibit the central region when asked to focus on the peripheral region. This deficit was correlated to the UFOV performance of divided attention (Kreither, Lopez-Calderon et al. 2017). Therefore, patients show a general inability to spread their attention to a number of inputs, and tend to process central inputs that are irrelevant to a greater extent, resulting in the inability to divide their attention in an adequate manner.

Cerebral Regions Associated With Attention

A number of regions are inappropriately activated during attentional tasks in patients compared to controls. Those regions include the dorsolateral prefrontal cortex (DLPFC), the insula, the anterior cingulate cortex (ACC), the parietal cortex, the amygdala, and the hippocampus (Carter, Bizzell et al. 2010).

The ACC is associated with sustained attention (Tamminga and Holcomb 2004), and failure to activate this region will impair input selection (Cameron S. Carter, Mark Mintun et al. 1997). The ACC is believed to detect mismatch and conflict, and is connected to the DLPFC to signal when a response should be improved (Lesh, Niendam et al. 2011). In short, the ACC could attribute valence to certain inputs, and the DLPFC could select appropriate responses according to the goal suggesting that the ACC could be activated during control of selection (Bench, Frith et al. 1993, Cameron S. Carter, Mark Mintun et al. 1997, Orellana and Slachevsky 2013). This is supported by studies, which reported that controls and schizophrenic patients had different ACC activation during decision-making tasks, such as the Stroop task (Henry H. Holcomb, Adrienne C. Lahti et al. 2000, Tamminga and Holcomb 2004).

The parietal cortex is also important for attentional processes. It is thought that the parietal cortex maintains possible responses linked to a particular stimulus, while the prefrontal cortex is involved in the selection of those responses (Bunge, Hazeltine et al. 2002). The parietal and DLPFC are also activated during sustained attention (Lesh, Niendam et al. 2011). Moreover, the parietal region is also required for attention switching (Lesh, Niendam et al. 2011) Supporting this, the parietal cortex, the ACC and

the DLPFC were observed as hypoactivated during the Stroop task in unmediated patients (Weiss, Siedentopf et al. 2007).

b) Verbal and Visual Learning and Memory

Verbal Memory and Learning. Verbal memory refers to the ability to remember words and phonological information. It is the ability to perceive information, store it, and retrieve it when necessary. For example, verbal memory is often used to remember events, ideas or facts. Impaired verbal learning and memory is a fundamental cognitive deficit in schizophrenia, and it has been extensively documented (Heinrichs and Zakzanis 1998, Toulopoulouand and Murray 2004, Bowie and Harvey 2006). Supporting this, Cirillo, Seidman, and colleagues (2003) reviewed 110 studies, and 101 of them showed that schizophrenic patients had a verbal memory deficit compared to controls, with negative studies mainly including other psychiatric disease, a small sample size, or patients diagnosed before the DSM-III. Verbal memory was found to be the greatest predictor of community outcome for schizophrenia patients (Michael Foster 1996, Green, Kern et al. 2004). This cognitive deficit is present during the premorbid phase, as well as in first-degree relatives and high-risk individuals (Cirillo and Seidman 2003). Verbal memory impairment is relatively stable throughout time, even though some studies show some small improvement, or decline (Toulopoulouand and Murray 2004).

The nature of the verbal deficits is still under debate. In their study, Cirillo, Seidman, and colleagues (2003) argued that the deficit in verbal memory was mainly due to an encoding deficit. Encoding is the first step of memory. It is necessary to create a representation of perceived information, which can then be stored. Cirillo, Seidman, and colleagues (2003) hypothesized that patients have trouble organizing inputs into semantic categories, but that the deficit would still be present even if the words could not be classified into groups. This ability to organize verbal inputs according to similar meaning is called semantic clustering. Semantic clustering is an encoding strategy in verbal memory, and is impaired in patients (Brebion, Amador et al. 1997, Gsottschneider, Keller et al. 2011). Supporting this hypothesis, a recent study showed that patients applied less semantic clustering in the California Verbal Learning Test (CVLT), resulting in a reduced performance in the patient group (Gsottschneider, Keller et al. 2011). Another

study showed that patients organizing words into semantic categories had better performance in immediate recall (Vaskinn, Sundet et al. 2008, Gsottschneider, Keller et al. 2011). Consequently, the encoding deficit seems to be related to inappropriate encoding strategies. Yet, patients could show less semantic clustering because of the requirement of higher cognitive demand during this process, or because they have trouble finding the similarities between the items (Brébion, David et al. 2004, Gsottschneider, Keller et al. 2011). Interestingly, Chan et al. (2000) found that providing an external cue about the categories in which words could be organised improved the performance of patients. This hints to the fact that patients could be unable to select an appropriate strategy by themselves. Moreover, this goes in line with a recent study by Ragland and colleagues (2015), which showed that when there were low cognitive demands, and that encoding strategies were given, patients did not show a deficit in a recognition task. Nevertheless, recall is more affected than recognition, which points to a deficit further than encoding. Moreover, when controlling for semantic clustering, Brébion et al. (2004) noted that the deficit was still present, suggesting that reduced encoding strategies did account for the whole verbal deficit, and that maintenance or retrieval might also be affected.

Visual Memory and Learning. Visual memory refers to the ability to remember visual information. This deficit was observed in schizophrenic patients, as well as first-degree relatives, although to a lesser extent than verbal memory and learning (Toulopoulou, Rabe-Hesketh et al. 2003, Skelley, Goldberg et al. 2008). The Rey–Osterrieth Complex Figure Test (ROFC) allows the assessment of visual memory and learning. This test consists of copying a complex figure, and then replicating it from memory, immediately or after variable delays (Kim, Namgoong et al. 2008). A deficit in immediate recall was observed in patients for this task, hinting to an encoding deficit (Seidman, Lanca et al. 2003). For instance, Seidman, Lanca et al. (2003) found that patients have a reduced ability to encode a picture as a whole, and tend to focus more on the details. This pointed to an organizational deficit during encoding, such as what is observed with the deficiency in creating semantic categories. The reduced organizational capacity finding was replicated (Kim, Namgoong et al. 2008), and related to the difficulty of the task (Glahn, Barrett et al. 2006). Furthermore, Seidman, Lanca et al. (2003) also

found that when controlling for the organizational deficit, the reduced recall persisted. In the same way, when testing immediate recall and controlling for organizational deficit, patients still present deficits which implies that the deficit is not only due to encoding dysfunction (Seidman, Lanca et al. 2003). Finally, it was suggested that patients give more importance to non-essential features, which reduces the attentional capacity to process significant part of the pictures (Seidman, Lanca et al. 2003, Kim, Namgoong et al. 2008). Therefore, as for verbal learning and memory, inappropriate strategies during encoding seem impaired, but other processes could also contribute to the deficit in visual learning and memory.

Cerebral Regions Associated With Verbal and Visual Memory

Verbal and visual memory deficits are attributed to a reduced communication and functional coupling between the prefrontal cortex and other regions such as the hippocampus, the thalamus and the cerebellum (Weiss and Heckers 2001, Toulopoulouand and Murray 2004). A reduction of the DLPFC gray matter was found in patients having verbal and visual memory deficits (Seidman et al., 1994). Accordingly, a meta-analysis by Ragland, Laird et al. (2009), showed that the most consistent finding was a reduction of lateral prefrontal activation during encoding and retrieval, suggesting its important role in memory deficits, and cognitive control (Ragland, Laird et al. 2009, Gsottschneider, Keller et al. 2011). Indeed, as stated, patients have trouble controlling and finding the right strategy to encode information, but the dysfunction will disappear if provided one. The lateral prefrontal cortex could thus be responsible for providing the appropriate strategy and control. Interestingly, the ventrolateral prefrontal (VLPLC) cortex and DLPFC cortex seem to be involved in different ways in verbal memory. Ragland, Laird et al. (2009) found that the VLPFC deficit disappeared when providing patients with encoding strategies, while the DLPFC deficit remained. The DLPFC is involved in organization, manipulation as well as monitoring the goal relevant information, and therefore crucial for task requiring flexibility and high cognitive processing. On the other hand, VLPFC is able to process semantic words that require less cognitive demand, or that are already in categories (Ragland, Ranganath et al. 2015). Therefore, an alteration in the DLPFC could impair encoding organization, and the VLPFC could compensate for the DLPFC during low demanding task. Some studies also

suggest that verbal deficits could also be attributed to hippocampal alterations, as this structure is involved in encoding and retrieval (Weiss and Heckers 2001). This hypothesis is noteworthy owing that the modification structure is one of the most consistent findings in patients (Seidman, Lanca et al. 2003). Finally, the reduced impairment of visual compared to verbal memory was attributed to a generally greater left hemisphere impairment in schizophrenia (Toulopoulouand and Murray 2004). Indeed, it is hypothesized that visuospatial processes are lateralized to the right hemisphere, while verbal processes are lateralized to the left hemisphere (Toga and Thompson 2003) .

c) Executive Functions: Cognitive Control and Flexibility

Executive functions refer to the capacity of understanding and using information in order to attain a goal (National Institute of Mental Health 2015). They include a variety of functions, which are important for goal directed behaviour and voluntary control (Bowie and Harvey 2006, Orellana and Slachevsky 2013). Executive functions help individuals plan, make analogies, solve problems, adapt to a changing environment, as well as execute many tasks at the same time in order to achieve a goal (Orellana and Slachevsky 2013). In short, executive functions could be considered as higher cognitive processes.

Executive function impairments are observed in a consistent manner throughout schizophrenia (Orellana and Slachevsky 2013). Those impairments have been known for a long time, as Kraepelin (1913) described patients as having lower mental efficiency, and a distracted mind (Orellana and Slachevsky 2013). As for other cognitive symptoms, they are present before onset, in first-degree relatives, as well as high-risk individuals (Orellana and Slachevsky 2013). Patients have low adaptive capacity to a changing environment, as well as inflexible thinking (Pantelis, Barber et al. 1999, Orellana and Slachevsky 2013). Executive function deficit can be assessed with the Wisconsin Card Sorting Test (WCST). This test requires individuals to shift rules according to the changing information provided by the evaluator. During this test, the rules of associations shift, and individuals must adapt according to feedback. It is important to note that attention is required during this test, as patients need to find the correct dimension,

reflecting rule selection. As mentioned before, patients have trouble rule selection when they are in competition. Nevertheless, perseveration, which measures the ability to change rule to use the correct dimension, measures cognitive flexibility, while inefficient sorting might reflect attentional processes (Greve, Williams et al. 1996). Indeed, the latter represents the selection of the appropriate action for a goal-directed behaviour, and will be deficient especially when there is competition of various possible responses. On the other hand, perseveration errors represent the inability to take into account perceptual information (Chambon, Franck et al. 2008), and change their behaviour according to the presented stimuli (Koechlin, Ody et al. 2003). It is known that patients have trouble in the inhibition of previously learned behaviours, which will cause increased perseverative errors, representing a loss of cognitive flexibility (Orellana and Slachevsky 2013). Finally, schizophrenia patients also perform poorly on the Tower of Hanoi test, and will take much more time and move to solve the task (Bustini, Stratta et al. 1999, Orellana and Slachevsky 2013). The Tower of Hanoi test consists of discs that must be displaced according to a set of rules in order to create a tower, and deficits in this task represent failure to plan, but also impulsive responding (Bustini, Stratta et al. 1999)

Cerebral Regions Associated with Executive Functions

Deficits in executive functions are related to hypofrontality, and the connection between the prefrontal cortex and other structures such as the basal ganglia, the medial temporal lobe, the parietal lobe and the ACC (Orellana and Slachevsky 2013).

The prefrontal cortex is connected to various regions, and it is thought that this structure integrates information, which can then provide top-down control (Lesh, Niendam et al. 2011). Indeed, the PFC serves as online storage (Miller 2001), and can compare incoming information with internal goals, in order to select appropriate responses (Lesh, Niendam et al. 2011). To achieve this, the PFC will provide bias to other structures in order to "guide" them (Miller 2001). Simplistically, the PFC can "decide" which information is required to attain a specific goal, and will bias the information towards the appropriate one (Lesh, Niendam et al. 2011). This function is mostly achieved by the DLPFC, which thought to be the crucial structure for maintenance of rules, and for response selection (Lesh, Niendam et al. 2011). A good example is the Stroop task, in which schizophrenic patients are deficient (Bench, Frith et al. 1993). The

cognitive control provided by the DLPFC is necessary in the colour-naming situation, in order to overcome the default action of word reading. Therefore, the DLPFC would be responsible for cognitive control, assuming a top-down regulation, and thus a central player in executive function (Koechlin, Ody et al. 2003, Orellana and Slachevsky 2013).

Furthermore, all cognitive manifestations pointed above, including attention, verbal, and visual memory deficits are also related to a prefrontal dysfunction, or to a reduced connectivity of this region with other regions. Indeed, the prefrontal cortex is connected to a number of other regions, such as the ACC, parietal regions as well as the medial temporal lobe (Lesh, Niendam et al. 2011, Orellana and Slachevsky 2013). The reduced connectivity and coupling between keys region in cognitive processing represents Bleuler's original thought about the disease. Schizophrenia means « split-mind», representative of the dysfunctional brain connections and integrative processes. Indeed, Bleuler thought that the decoupling of various functions was the main cause of the disease (van den Heuvel and Fornito 2014, Sakurai, Gamo et al. 2015). As mentioned above, attentional deficits are linked to prefrontal, ACC and parietal disconnection. On the other hand, visual and verbal learning and memory are linked to a prefrontal dysfunction, and reduced hippocampal connectivity. Therefore, the prefrontal cortex, and its connectivity seem to be primordial for the cognitive symptoms. This goes back to Kraepelin (1971) describing dementia praecox as "an orchestra without a conductor" (Lesh, Niendam et al. 2011). Interestingly, patients without medication show hypofrontality, which means it is inherent to the disease (Sakurai, Gamo et al. 2015). Moreover, even though cognitive symptoms seem sparse, the failure to control and self-regulate seems to be a shared characteristic.

Thus, numerous cerebral regions involved in cognitive deficits seem to display altered activation in schizophrenia. Interestingly, numerous anatomical modifications are reported in patients with schizophrenia. This could underpin a number of deficits, as functional activation has been linked to structural integrity (Guye, Parker et al. 2003, Greicius, Supekar et al. 2008, Bennett and Rypma 2013). A quick review of anatomical findings in schizophrenia will thus be presented below.

Anatomical Alterations in Schizophrenia

Alterations in gray matter such as cortical thickness or density, as well as alterations in white matter connecting various regions have been reported in schizophrenia (Wheeler and Voineskos 2014). First, an overview of the values used to measure gray and white matter integrity will be exposed. This will be followed by anatomical findings in schizophrenia, which could be linked to cognitive deficits.

Gray matter volume can be represented by cortical thickness and surface area (Xiao, Lui et al. 2015). Cortical thickness represents the distance between the white matter and the pial surface, the latter being the surface between gray matter and cerebrospinal fluid (Ehrlich, Brauns et al. 2012). Compared to surface area, cortical thickness is more representative of the microstructural arrangement, as it represents cytoarchitectural features (Ehrlich, Brauns et al. 2012, Xiao, Lui et al. 2015). Changes in neurogenesis, migration of neurons, and density affect cortical thickness values. As schizophrenia is thought to be a neurodevelopmental disease, changes in cortical thickness are thought to better represent alterations occurring during disease development (Rapoport, Addington et al. 2005). On the other hand, white matter integrity can be explored through diffusion-weighted imaging (DWI). Simply put, this imaging technique is based on Brownian motion, which stipulates that free water will move in random directions. Free water will have an isotropic movement, meaning that it will diffuse equally in all direction, a diffusion movement which can be represented by a sphere (Descoteaux and Poupon 2012). This is the case for example in the cerebrospinal fluid, in which water is not restricted. However, this is not the case for water present in white matter, as fibres are organized in parallel, and will restrict water diffusion. Water movement will therefore have a preferential diffusion direction, which is referred to as anisotropic, and can be illustrated by a 3D ellipsoid (Catani and de Schotten 2012). With this technique one can thus obtain various values such as fractional anisotropy (FA). FA is a value that represents the index of anisotropy, and indirectly measures the integrity of fibres. This value ranges from zero to one, representing the integrity and coherence of a fibre. A value of zero represents an isotropic movement. Therefore, a low FA corresponds to a less compact fibre, as water would be less restricted, while a high FA

corresponds to a denser and intact fibre, as water would be diffusing in a preferred direction.

Cortical thickness reductions in schizophrenia are broad, and are found in the frontal, temporal, occipital and parietal areas mostly (Kuperberg, Broome et al. 2003, Gogtay, Greenstein et al. 2007, Goldman, Pezawas et al. 2009, Ehrlich, Brauns et al. 2012, Xiao, Lui et al. 2015). There is no consensus concerning cortical thickness in schizophrenia. As a matter of fact, although most studies report decreased cortical thickness values in patients compared to controls, increased values have also been reported (Levitt, Bobrow et al. 2010, Wheeler and Voineskos 2014, Canu, Agosta et al. 2015). Nevertheless, cortical thickness study is important, as its integrity has been related to numerous cognitive tasks such as verbal memory (Dickerson, Fenstermacher et al. 2008), item recall and recognition, as well as manipulation in healthy controls (Ehrlich, Brauns et al. 2012). On the other hand, numerous studies also show that the relationship between cognition and cortical thickness is lost in schizophrenia (Ehrlich, Brauns et al. 2012).

As for gray matter studies, white matter integrity studies in schizophrenia are also heterogeneous. Temporal and frontal white matter reductions seem to the most consistent findings in chronic patients (Kubicki, McCarley et al. 2007, Kyriakopoulos, Bargiotas et al. 2008, Ellison-Wright and Bullmore 2009). A meta-analysis which combined 15 DWI studies in schizophrenia observed a FA reduction in 112 coordinates in patients compared to controls (Ellison-Wright and Bullmore 2009). Reduction of the white matter connecting the left deep frontal and deep temporal cortices were the most consistent (Ellison-Wright and Bullmore 2009). Likewise, a review reported that reduction in fibres connecting prefrontal and temporal lobes such as the uncinate, cingulum and arcuate fasciculus were the most consistent observations in chronic patients (Kubicki, McCarley et al. 2007). Nevertheless, studies also found increased FA in fibres connecting those regions (Knöchel, O'Dwyer et al. 2012, Wheeler and Voineskos 2014). Furthermore, studies including first episode patients are less consistent (Wheeler and Voineskos 2014). Alterations are usually more widespread in this population, and they mostly show reduction in the prefrontal, temporal and parietal lobe (Wheeler and Voineskos 2014).

Finally, white matter study has also been correlated with various cognitive measures in schizophrenia (Nestor, Kubicki et al. 2004, Kubicki, McCarley et al. 2007). For instance, FA values have been correlated with executive function, and performance monitoring (Kubicki, Westin et al. 2002, Nestor, Kubicki et al. 2004).

Therefore, gray and white matter morphology findings in schizophrenia are very heterogeneous. A number of factors could explain the inconsistent findings. The clinical presentation of schizophrenia itself is heterogeneous, as patients will present various symptoms in various degrees. Moreover, schizophrenic patient population has a number of moderator variables which are difficult to account for such as age of onset, medication, or socio-economic status, as various populations are included in various studies (Wheeler and Voineskos 2014). Finally, the aetiology of schizophrenia is diverse, and the brain alteration would be representative of the various genetic or environmental causes (Wheeler and Voineskos 2014).

Taken together, cognitive symptoms as well as anatomical modifications are broad and are expressed to a different degree across the patient population. Various cognitive symptoms have been linked to altered anatomy, but results are heterogeneous. As cognitive disruptions in schizophrenia are broad, it would be would be advantageous to link a specific deficit to specific anatomical modifications. Accordingly, one function that encompasses a high number of cognitive processes is working memory. Indeed, in order to successfully use this function, one must maintain goal information, in order to guide the behaviour towards the right action. This process not only touches memory, but also attention, and is considered a central executive function. Therefore, the crucial working memory function will be described in the next section.

3. Working Memory

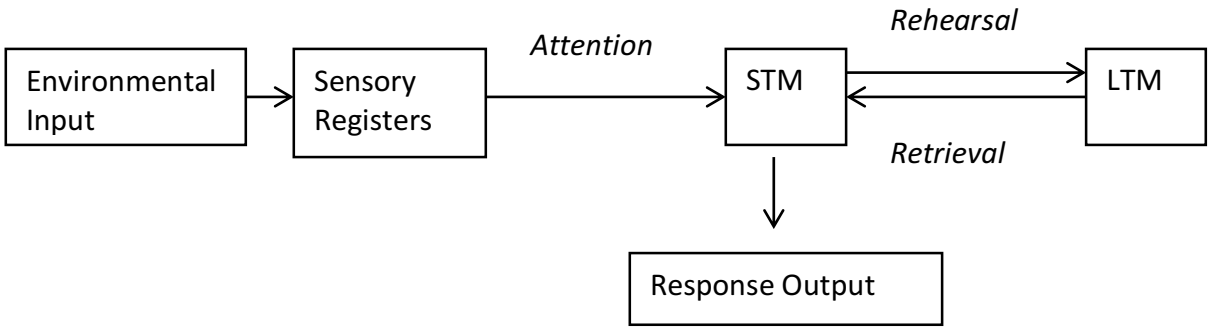
Working memory is essential to everyday life. This function allows the temporary maintenance and manipulation of a limited amount of information. It enables individuals to complete various complex cognitive tasks, such as reasoning, comprehension, learning, and spatial processing (D'Esposito, Postle et al. 2000, Baddeley and Hitch 2010).

Manipulation can occur on old information, such as using long-term memory (LTM) knowledge to solve a particular problem, or on new information in order to integrate new complex memories into LTM. It thus provides a function located between perception, action, and LTM (Baddeley 2003).

a) Models

Three main working memory models have been developed throughout the years. First of all, for many years, the multistore model of Atkinson and Shiffrin was used for STM (Figure 2) (Atkinson and Shiffrin 1968). Their model was quite simple, and composed of a sensory register, short-term memory (STM), and LTM. Importantly, this framework was linear. To describe it briefly, information was perceived by sensory organs, and attention allowed particular inputs to enter storage in STM (Atkinson and Shiffrin 1968). Information could be maintained in STM for a limited amount of time, after which decay would occur. Maintenance in STM could also be increased with rehearsal. Their short-term store was also called working memory, and had a role in cognition. Furthermore, STM was an indispensable passage for the storage or retrieval of information from LTM (Baddeley 2000). Finally, the last component of this model was LTM, in which there was no decay, and no capacity limits

Figure 2: *Figure Adapted From Atkinson and Shiffrin Model (1971)*



A number of observations went against the Atkinson and Shiffrin model. The main argument against it was the conception that access to STM was crucial for storage and retrieval from LTM (Baddeley 2010). Consequently, their model could not account

for the fact that some patients with deficient STM have normal LTM (Baddeley 2000, Baddeley 2012). It also implied that any information maintained long enough into STM would access LTM, which did not account for the fact some information, for example deep encoding and more elaborate learning, is stored much more easily into LTM (Craik and Lockhart 1972, Baddeley 2000). Finally, their model stated that STM was important for cognition, implying that every individual with a STM deficit would cognitively impaired, and which is not the case (Baddeley 2000). One example of this is patient PV, a patient with a very small digit span, but with certain number of conserved learning abilities (Baddeley, Papagno et al. 1988).

In an attempt to explain the discrepancy in the STM field, Hitch and Baddeley introduced the multicomponent model in 1974, and developed the concept of working memory (Baddeley and Hitch 1974). Instead of the simple unitary STM, they introduced a model in which information would be stored and manipulated in different compartments, according to their modality and characteristics (Baddeley 2012). In short, the authors kept the differentiation between LTM and STM, while expanding the STM concept. The model also kept the idea that LTM can store and unlimited amount of information, which could later be recalled, by re-entering STM (Rottschy, Langner et al. 2012)

The multicomponent model was developed following one experiment by Baddeley and Hitch (1974). In that study, participants were asked to perform an executive task, such as visual grammatical reasoning, while their working memory was overloaded with a digit span task. Surprisingly, participants were still able to perform the executive task while recalling numbers (Baddeley 2012). As reasoning was not overloaded by the storage of multiple digits, this pointed to a non-unitary system, with limited storage systems controlled by an "executive system" (Baddeley and Hitch 1974, Baddeley 2012). Moreover, participants were able to perform the visual and verbal tasks at the same time, which suggested separate storage for verbal and visual information. Thus, their initial model involved three components, two "slave" systems: the phonological loop and the visuo-spatial sketchpad, which were controlled by the central executive (Baddeley and Hitch 1974, Baddeley 2012). Those three components will be briefly described below.

The **visuo-spatial sketchpad** is important for the temporary and limited maintenance of visual and spatial information (Baddeley 2010). Retrieval of visuo-spatial information from LTM is also one of its functions. For example, when someone is asked to count how many doors are in their house, they would use, among other things, the visuo-spatial sketchpad to "artificially" navigate throughout their house (Baddeley and Hitch 2010). As mentioned, the sketchpad has a limited capacity (Baddeley 2012). One way to study its capacity is the Corsi test, in which the experimenter shows an increasing sequence of blocks, and the subject needs to reproduce it until they can't perform anymore. This span is usually three to four (Todd and Marois 2004). Finally, even though visual and spatial information are confined to the same compartment in this model, those two modalities are separated, and can be affected in a different way (Klauer and Zhao 2004, Baddeley 2012). This was inferred by the fact that visual tasks only interfere with visual memory, while spatial tasks only interfere with spatial memory (Baddeley and Hitch 2010). For example, in one study, subjects were required to remember either the spatial location (i.e. spatial memory) or the form of an object (i.e. visual memory) (Tresch, Sinnamon et al. 1993). The spatial memory task was impaired when performing a movement discrimination task, while the visual memory task was impaired when performing a colour discrimination task (Tresch, Sinnamon et al. 1993).

The other component, the **phonological loop**, is important for the temporary maintenance of speech-based information (Baddeley 2000). This component is composed of two features, the phonological store and the articulatory rehearsal component (Baddeley 2000). The phonological store has a limited capacity, is able to hold information for about 2 seconds, has a serial span of five or six, and is responsible for speech perception (Baddeley 2012). On the other hand, the articulatory loop is useful for rehearsal, and is responsible for speech production. A number of observations supported the existence of a phonological store. First, blocking rehearsal, for instance by repeating unrelated words, will impair immediate recall, a phenomenon called articulatory suppression (Baddeley 2010). This supports the idea that rehearsal has a central role in maintenance and refreshment of a speech trace. Second, the word length has an effect on

memory, as longer words are easier to forget (Baddeley, Thomson et al. 1975, Baddeley 2000). This could be due to reduced rehearsal, as this process it assumed to happen in real time. Indeed, longer words would take longer to pronounce, thereby reducing rehearsal (Baddeley 2000). Supporting this, when articulatory suppression occurs, maintenance capacity for short and long words is equal (Baddeley 2012). Lastly, learning a list containing similar sound will impair immediate recall, yet, words having the same meaning won't impair recall. This thus implies that there is a possible phonological code (Baddeley 1966, Baddeley 2000, Baddeley 2010).

The **central executive** controls the two other storage systems, and provides attentional control. It can distribute prioritized information to the storage systems, it is able to perform cognitive tasks, as well as transfer information into LTM (Baddeley 2012). It has a limited processing ability, and does not have any storage capacity (Baddeley 2012). The main characteristics are its ability focus, and divide its attention. Moreover it is responsible for task switching, as well interacting with LTM (Baddeley 2012). A good example would be driving a car in which the habitual route is not accessible due to roadwork. The central executive would be needed in order to focus the attentional system, and interact with the visuospatial sketchpad in order to visualize possible route and decide which other option is the best to get to a destination (Baddeley and Hitch 2010). It thus has the role of controlling and selecting attentional resources, strategies, as well as coordinating the information of the passive storage systems (Park and Gooding 2014). Importantly, without this compartment behaviour would be distractible, perseverative, stereotypic, and would be unable to take context into account (Park and Gooding 2014).

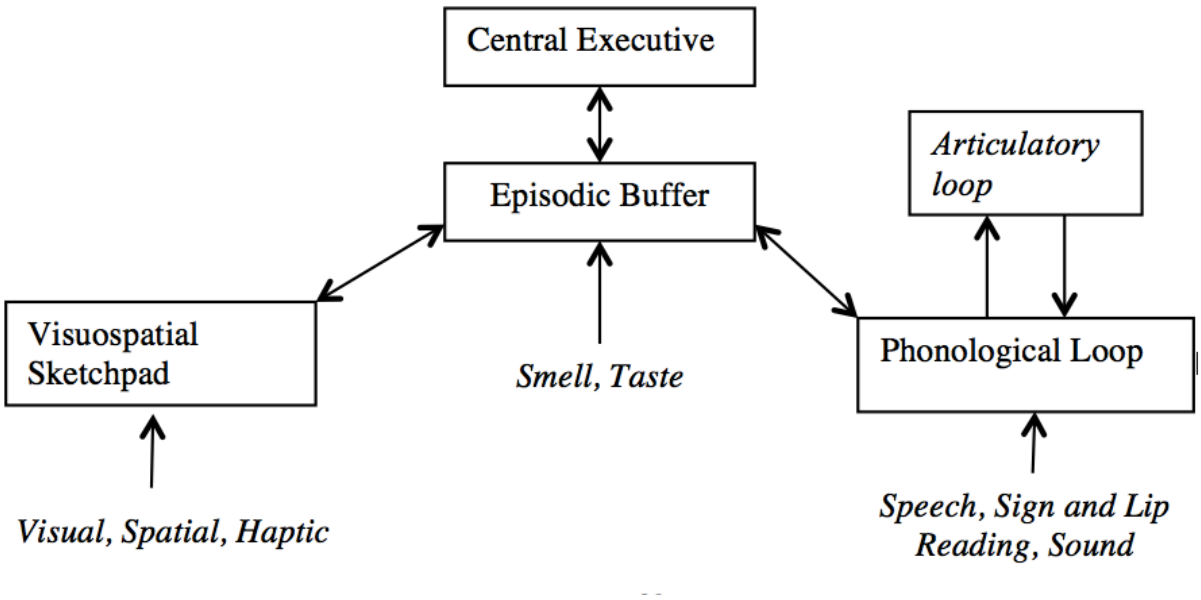
Still, the model presented above did not account for numerous observations. For example, when recalling unrelated words, the span is usually five to six words. Yet, when it is meaningful, such as a sentence, the span goes up to sixteen (Baddeley 2012). This suggested a link with semantic knowledge and LTM, as well as an integration of phonological information (Baddeley 2012). Therefore, the new model included a link between the storage systems and LTM, which was not originally present in the model.

Moreover, other observations also suggested that there might be an additional component, such as integrative processes. Indeed, phonological (e.g. various words) or visuospatial (e.g. color and shape) information could be integrated in their respective compartment (i.e. the visuospatial sketchpad, and the phonological loop). Yet, this model did not account for integration of phonological and visuospatial information (Baddeley 2000). Indeed, in one study participants were asked to recall a digit span of visually presented numbers while performing articulatory suppression (Baddeley 2000). The experimenters expected reduced performance, as rehearsal of irrelevant words would prevent the encoding of the digits in the phonological loop. However, performance was only mildly reduced. As the central executive has no storage capacity, the integration of phonological (word representing the number) and visual information (visual number) information would occur somewhere else. Moreover, as the visuo-spatial sketchpad is not considered suitable for serial recall, this implied that another component was able to integrate, store and recall the visually presented digits (Baddeley 2000).

Therefore, a new component, the **episodic buffer**, was added to the model (Figure 3). This component provides a link between LTM, the two storage systems, and the central executive (Baddeley 2000). Those links allow this new compartment to perform the process called binding. Binding allows information coming from different sources to be integrated into a complex representation (Baddeley 2000). The episodic buffer can therefore create and temporarily hold complex information in a multimodal code, with a limited capacity of about four "chunks" (Baddeley 2000, Baddeley 2010). For example, it provides the ability to integrate into LTM a complex event, including its various visual features, sounds, and phonological information in order to have a detailed memory. Therefore, it is important for episodic memory, as it integrates various information of a scene in order to create a coherent representation in memory. On the other hand, it also provides the ability to retrieve this complex knowledge from LTM, in order to solve a current problem. The episodic buffer was first believed to operate only under the control of the central executive, yet, it became clear that binding could be automatic (Baddeley 2010). This was suggested by a study which showed that even when "overloading" the central executive, binding could still occur (Baddeley, Allen et al. 2011). In that study, one condition required participants to perform a single feature visual

memory task while completing a verbal task. In the other condition, a visual binding memory task was combined with a verbal task. The logic was that the verbal task would deplete the central executive's resources, which would allow experimenters to determine which visual task was most affected by reduced attentional resources. Both visual task performances were reduced when simultaneously completing the verbal task. However, visual binding performance was affected in the same way the visual single feature performance was. This implied that binding did not necessitate more central executive attentional resources than simple visual feature memory (Baddeley, Allen et al. 2011). Therefore, binding could also occur in a passive way, without the control of the central executive. However, it is important to mention that Baddeley and colleagues (2010) did not exclude that the buffer also has an active function as well.

Figure 3: *Figure Adapted from Revised Working Memory Model, Baddeley (2011)*



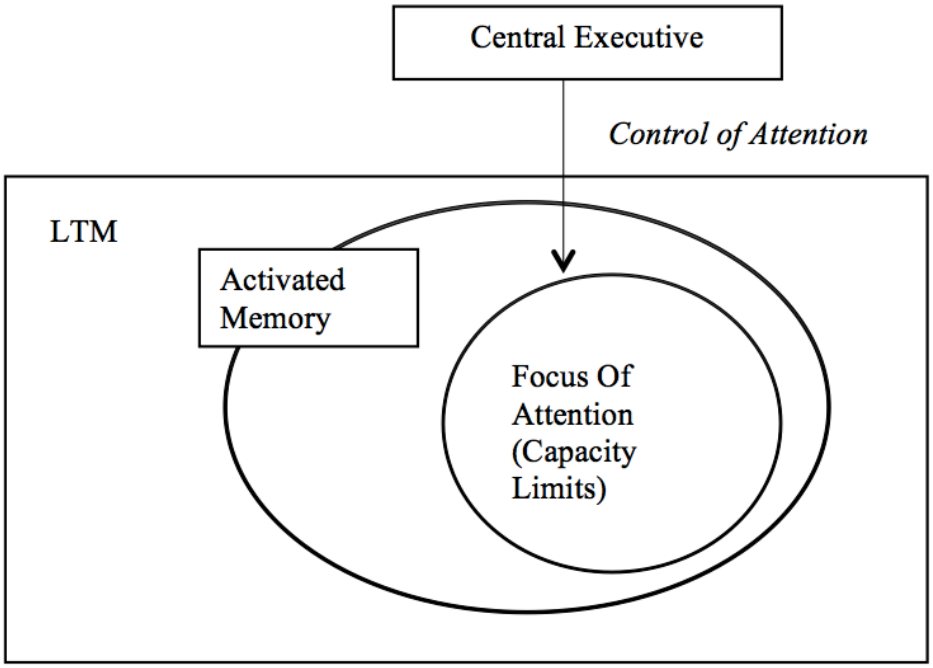
Finally, **Cowan's model** of working memory is another influential model (Figure 4). As in other models, STM has limited storage capacity while LTM storage is unlimited (Cowan 2008). Yet, unlike Baddeley's Model, STM is not composed of several subcomponents, but of an activated memory and a focus of attention. Sensory information as well as LTM information can enter activated memory through the focus of

attention, and can be maintained in the active state with rehearsal (Cowan 2008). Moreover, sensory information can activate LTM, leading to "activated LTM".

Activated memory allows the passive storage of information. Yet, unlike the phonological loop and the visuospatial sketchpad of Baddeley's model, activated memory has no limits in the amount of information it can maintain. Indeed, the storage limit in working memory would not be due to storage limits, but to interference. Hence, unlike Baddeley's model, Cowan's model assumes the temporary maintenance is due to interference between information of the same modality. Therefore, instead of two compartments which would get filled up individually (i.e. phonological loop and visuospatial sketchpad), information having the same modality would only interfere with each other (Cowan 1988).

On the other hand, the attentional focus allows the active treatment of information. A limited amount of information can be held by the focus attention, and this component is similar to the episodic buffer (Cowan 2008). Indeed, Cowan also proposed that working memory could allow the combination of information into "chunks", and that "chunking" could be used as a strategy to increase the limited STM capacity (Cowan 2008). Like Baddeley's model, the capacity is about four "chunks" (Cowan 2001, Cowan, Elliott et al. 2005). However, the limit of "chunks" is determined by the capacity to pay attention of those representations (Cowan 1988, Cowan, Elliott et al. 2005, Cowan 2008). Finally, the central executive can control the focus of attention. Therefore, this component proposed to represent a number of higher cognitive functions, which are similar to the component of the same name in Baddeley's model, and is required, for example, to inhibit distractions, and other higher executive functions (Cowan 1988).

Figure 4: *Figure Adapted from Cowan's Working Memory Model (Cowan 2009)*



All in all, working memory is a complex cognitive function, which is crucial to perform everyday tasks. Several models have attempted to explain this process, but all agree that this function requires the interaction of attentional resources, executive processes, cognitive control and flexibility, as well as visual and verbal memory. As mentioned before, those processes are all impaired in schizophrenia, which hints to the fact the working memory itself could also be dysfunctional in patients. Accordingly, working memory deficits in schizophrenia will be discussed in the next section.

b) Working memory Deficit in Schizophrenia

Working memory is a core deficit in schizophrenia. As for other cognitive symptoms, working memory deficits have been found in first-degree relatives (Heather M. Conklin, Clayton E. Curtis et al. 2000, Lee and Park 2005, Park and Gooding 2014). They are present irrespective of the state of the disease, develop during the premorbid phase, and are a predictor of functional outcome (Green 1996, Gazzaley, Rissman et al. 2004, Park and Gooding 2014). Those observations all point to the fact that working memory deficits are a cause, and not a consequence of the disease. Moreover, working

memory impairments in schizophrenia are observed even when controlling for IQ and education (Park and Holzman 1992, Lee and Park 2005). This is important, as working memory deficits do not simply result for lower IQ and could represent an underlying pathology of schizophrenia.

Patients have deficits in all modalities including spatial, verbal, auditory, object and haptic working memory (Gazzaley, Rissman et al. 2004, Lee and Park 2005). Moreover, those deficits are present irrespective of the methodology. Indeed, Lee and Park (2005) conducted a meta-analysis which combined 124 working memory studies with schizophrenic patients. The main goal of this meta-analysis was to determine whether working memory deficits were present independently of the task. This is important, as it would suggest that working memory could be a core deficit in schizophrenia, and that the impairment is not simply due to specific aspects of certain tasks. Studies included tests such as delayed response task, delayed matching-to sample task, as well as N-back task. Delayed response task is a test in which a stimulus is presented, and after a delay, subjects need to recall a characteristic of that object (e.g. location or colour). On the other hand, delayed matching-to sample task is a test in which a stimulus is presented, and after a delay, subjects need to identify which is the sample stimulus among novel stimuli. Finally, N-back task is a test that requires subjects to recall if the current presented stimuli were presented *N* trials before. In short, all tasks require adequate representation, manipulation, and updating of information in memory. The authors found deficits in all tasks including verbal and visuospatial working memory, with an effect size of 0.45 (Lee and Park 2005). Importantly, the authors found that those deficits were independent of methodology, suggesting that working memory deficits go beyond specific modalities. However, it is important to mention that visuospatial deficits had a higher effect size and robustness (effect size: 0.46, coefficient of robustness: 2.92) than the verbal domain (effect size: 0.45, coefficient of robustness: 2.31) (Lee and Park 2005).

As the deficits are present across modalities, it could be advantageous to focus on the temporal characteristics of working memory to truly understand the aetiology of this impairment (Lee and Park 2005). Indeed, in order to attain a goal, it is necessary to encode, internally represent, maintain, and manipulate the information while inhibiting

distractors, as well as retrieve the appropriate information when needed (Lee and Park 2005). Deficits could occur at any of those phases, yet, most studies report an encoding or maintenance deficit (Lee and Park 2005, Johnson, Morris et al. 2006, Driesen, Leung et al. 2008, Schlösser, Koch et al. 2008, Anticevic, Repovs et al. 2011, Anticevic, Repovs et al. 2012, Mayer and Park 2012, Park and Gooding 2014), while retrieval deficits have not been documented to a great extent. Indeed, even though some retrieval studies have been conducted, authors hint to the fact that altered activation during this phase could be due to improper encoding or maintenance of the stimuli in the first place (Zhao, Tan et al. 2011). Yet, one study showed that first-degree relatives presented compensatory activation compared to patients during retrieval which increased their performance (Lynn, Kang et al. 2016). This thus inferred that retrieval deficits are present in the schizophrenic population. Nevertheless, deficits in encoding or maintenance have been more extensively documented, and a deficit in those phases could result in a working memory deficit encompassing all tasks and methodologies, as observed in the meta-analysis by Lee and Park (2005). This possibility will be explored below.

Encoding

A number of observations suggest that schizophrenic patients have an encoding deficit (Lee and Park 2005, Hahn, Robinson et al. 2010, Mayer and Park 2012). For example, the meta-analysis by Lee and Park (2005) reported no effect when increasing the delay period, suggesting that information might not properly be formed as a mental representation initially. However, it is unclear why encoding processes would be impaired, and two main hypotheses were posited to explain this dysfunction. Failure to properly encode the target could either be due to an altered perception, or to inappropriate target selection due to attentional impairment (Park and Gooding 2014). This difference is important as it distinguishes between the general reduced ability to form a mental representation, and the inability to properly select the appropriate target, implying that formation of mental representation itself would be spared. Several studies suggest that the dysfunction would be due to impaired attentional processes. For example, increasing target valence minimizes the need for attentional control. Accordingly, Lee & Park (2002) found that increasing input valence improved performance, which implied that encoding deficit could be due to reduced attentional control. This was later supported by

another study, which observed that inability to inhibit distractions impaired encoding in patients with schizophrenia (Hahn, Robinson et al. 2010). This thus implies that patients have a difficultly to overcome salient distractors, which impairs adequate target encoding. Finally, another argument supporting a deficit in attentional processes is the presence of false memories in unaffected relatives, and patients with schizophrenia (Mayer and Park 2012). Indeed, perception impairment would lead to defective encoding and result in a low confidence during retrieval. On the other hand, impaired attention would lead to effective encoding of the wrong target. This would result in confidence of the response, leading to false memories, a phenomenon that has been reported in schizophrenia (Mayer and Park 2012, Park and Gooding 2014). Therefore, the presence of false memories in the schizophrenic population hints to the fact the formation of mental representations is spared, yet, due to impaired attentional processes, inappropriate information would be encoded into memory.

Maintenance

In schizophrenia studies, even if encoding is controlled for, working memory deficits are still present (Tek, Gold et al. 2002, Kim, Park et al. 2006). This implies that the dysfunction goes beyond encoding deficits (Lee and Park 2005). Maintenance is the ability to retain a representation formed during encoding throughout a delay. In order to achieve maintenance, one must direct their attention to external or internal information. Attentional processes are thus crucial to maintain the internal representation during a delay. It is hypothesized that patients have reduced attentional control, and fail to focus on internal representations during the delay, which reduces maintenance (Park and Gooding 2014). Reduced attentional control could also increase distractibility. Indeed, patients display an inability to block distractors, which could deviate attention from internal representations (Park and Gooding 2014). On the other hand, Park and Lee (2005) observed that increasing the delay after 1 second did not worsen the working memory deficit in patients, which would suggest that maintenance is spared. However, they do not exclude the possibility of a reduced early maintenance capacity. Indeed, as there is vulnerability in the first second, this could suggest that early maintenance might be more susceptible to dysfunctions (Lee and Park 2005). This might be explained by the additional manipulation requirement. Indeed, deficits in simple maintenance studies, such

as a recognition tasks or simple digit span tasks are heterogeneous, with some studies observing deficits (Spindler, Sullivan et al. 1997, Kim, Glahn et al. 2004, Keedy, Ebens et al. 2006) and some not observing any (Park and Holzman 1992, Morice and Delahunty 1996, Frydecka, Eissa et al. 2014). Yet, when manipulation is required, a deficit is usually present (Kim, Glahn et al. 2004, Cannon, Glahn et al. 2005). For example, a study required patients to perform two tasks, with one task requiring simple maintenance of information, and the other requiring both manipulation and maintenance (Kim, Glahn et al. 2004). Results showed that patients have a deficit both in maintenance and manipulation, but that manipulation is affected to a greater extent (Kim, Glahn et al. 2004). This could be due to the fact that adequate maintenance is required for manipulation. Indeed, a recent review (Park and Gooding 2014) argued that maintenance and manipulation are actually part of the same process, as the same network supports the two functions (Leung, Gore et al. 2002). The authors argue that "active attention" is a core function of manipulation, a crucial property also necessary for maintenance. For this reason, they propose that maintenance and manipulation should not be treated as completely two independent processes (Park and Gooding 2014). Therefore, patients could have a deficit in maintenance, which would be exacerbated when manipulation is required.

In summary, schizophrenic patients seem to be impaired across all working memory tasks. Those deficits would mainly be due to an encoding deficit, but maintenance could also contribute to this dysfunction, especially when manipulation is required. If applying this to Baddeley's model, a deficit in the central executive, responsible for cognitive and attentional control, could be responsible for this inappropriate target encoding, as well a maintenance and manipulation deficits in patients (Barch and Ceaser 2012, Park and Gooding 2014). Furthermore, as this deficit is consistent across tasks, it would be adequate to identify the core network involved across all working memory tasks in healthy controls. Indeed, if this network were altered in schizophrenia, it could represent the underlying cause for this specific deficit.

c) Cerebral Regions Associated with Working Memory:

A number of regions have been associated with working memory, but the exact network is still under debate. Working memory is complex, and it is therefore difficult to understand the importance of each region in each specific process. Yet, the prefrontal and parietal cortex are often involved in working memory studies. Accordingly, there will be a brief review of this network in healthy subjects, followed by its role in schizophrenia.

The Prefrontal-Parietal Network

In healthy controls, the prefrontal-parietal network is constantly recruited during working memory tasks. Indeed, a meta-analysis combining 198 fMRI studies on healthy subjects observed that the fronto-parietal network was constantly activated, independently of the tasks (Rottschy, Langner et al. 2012). This is important, as it implies that this network is not related to any specific aspect of a working memory task, but to the general working memory performance. Moreover, this finding replicated results from a previous meta-analysis which combined N-back tasks studies (Owen, McMillan et al. 2005). In that meta-analysis, prefrontal cortex activation was often accompanied by parietal lobe activation, particularly Brodmann area (BrA[2]) 7 and 40 (Owen, McMillan et al. 2005). This led the authors to suggest that the prefrontal-parietal network would be necessary for all N-back tasks, while the methodological variations would recruit differential cortical areas.

Interestingly, the prefrontal-parietal network is related to a number of crucial processes required for working memory such as encoding, manipulation, and maintenance. First, this network is important for maintenance, as it is responsible for attentional processes. Indeed, the parietal cortex distributes attentional processes, while the prefrontal cortex controls the allocation of attention (Sharma, Weisbrod et al. 2011, Park and Gooding 2014). Moreover, the parietal cortex is thought to store verbal and visuo-spatial information, while the lateral PFC is important for directing the attention towards internal or external representations (Müller and Knight 2006, Rottschy, Langner et al. 2012, Park and Gooding 2014). Therefore, simultaneous activation of the prefrontal and posterior parietal cortex could be responsible for maintaining representations that are

[2] BrA is used instead of BA to avoid confusion with the active binding abbreviation (Ba)

not in the field of view anymore (Gazzaley, Rissman et al. 2004). This is consistent with the effect of working memory load on the prefrontal cortex, as it will interact with the parietal system in different degrees depending on task demands (Rottschy, Langner et al. 2012). This network is also important for manipulation. As mentioned, maintenance and manipulation share similar anatomical regions, yet they differ functionally, with manipulation recruiting the DLPFC to a greater extent, and maintenance recruiting VLPFC to a greater extent (Owen, Evans et al. 1996, D'Esposito, Aguirre et al. 1998, Glahn, Kim et al. 2002, Veltman, Rombouts et al. 2003). Finally, the DLPFC also has important roles during encoding such as response selection, as well as strategy implementation and evaluation (Owen, McMillan et al. 2005). For example, D'esposito, Postle, and colleagues (2000) found in their study that the DLPFC is activated when there is a high information load, which might reflect the activation of efficient encoding. Indeed, when information needs to be organized into "chucks" to facilitate their memory and reducing the memory load, an increased activation of the lateral prefrontal cortex is seen (Owen, McMillan et al. 2005). Therefore, this circuit would be necessary to encode the appropriate external target, as well as maintaining and manipulating its representation in memory in order to accomplish a working memory task (Leung, Gore et al. 2002, Park and Gooding 2014).

Lastly, the prefrontal-parietal network might represent the central executive as presented in Baddeley's model (2010), as it would be essential to keep focus on the appropriate information in order to attain a goal (Rottschy, Langner et al. 2012). Of course, working deficits are not limited to a modification of the prefrontal-parietal network. Depending on the various specific aspects of the tasks, those deficits are caused by spread alterations in connectivity between regions (Gazzaley, Rissman et al. 2004, Rottschy, Langner et al. 2012, Park and Gooding 2014). Nevertheless, as the prefrontal-parietal network is involved independently of the task, it could imply that a deficit in this network would impair most working memory tasks. This is interesting, as impairment of this network would adequately represent the core working memory deficit in schizophrenia.

The Prefrontal-Parietal Network in Schizophrenia

Numerous observations suggest a prefrontal-parietal network deficit in schizophrenia. Moreover, an impairment in the activity of this network could underlie both encoding, maintenance, and manipulation impairments. As a matter of fact, encoding deficits in schizophrenia have been related to dysfunctions of this network (Meda, Stevens et al. 2009). A reduced activation of the frontal-parietal network during encoding was observed in patients compared to control, and related to working memory deficits (Meda, Stevens et al. 2009). Moreover, the prefrontal-parietal network is required, in part, for top-down attentional control. This process is important during encoding in order to select appropriate information among various stimuli (Mayer, Fukuda et al. 2012). Indeed, this process is in part regulated by prefrontal cortex which can control which information can be stored or attended to in the parietal cortex (Mayer, Fukuda et al. 2012). Therefore, alteration in the prefrontal-parietal network could also lead patients to store irrelevant information during encoding, which is, as mentioned, linked to working memory deficits (Mayer, Fukuda et al. 2012). Furthermore, inappropriate top-down control due to reduced prefrontal-parietal coupling could also lead to maintenance deficits. For instance, it was found that patients have an inability to resist distractors (Mayer, Fukuda et al. 2012). In fact, DLFPC activation was related to distraction resistance during the maintenance phase in healthy individuals, but not in patients with schizophrenia (Anticevic, Repovs et al. 2012). Lastly, deficits in manipulation have been linked to aberrant prefrontal activation. For example, Cannon, Glahn et al. (2005) conducted a spatial working memory study with 11 patients and 12 controls, which included a condition requiring only maintenance, and another condition requiring both maintenance and manipulation. The authors observed that there was a reduced DLPFC activation in patients compared to the control group in the task that required manipulation. Moreover, the reduced DLPFC activation was linked to the deficit in the patient group. This finding also applies to verbal working memory. Indeed, Hao-Yang Tan, Wei-Chieh Choo et al. (2005) conducted a study with first-episode schizophrenic patients, which required maintenance in one condition, and maintenance and manipulation in the other. Both the patient and the control group showed left frontal-parietal network activation during maintenance and manipulation, but the patient group

had a reduced DLPFC activation in both conditions. Moreover, this reduction was even more pronounced for the condition requiring manipulation (Hao-Yang Tan, Wei-Chieh Choo et al. 2005). Therefore, both those study support the hypothesis that manipulation would be affected to a greater extent in the schizophrenic population than maintenance, and that the prefrontal-parietal network would be required for both those processes.

All those observations point to the importance of the integrity not only of the prefrontal and parietal cortex, but also of their connectivity. Indeed, inappropriate connectivity in this network could lead to deficits in a number of processes in schizophrenia. This hypothesized reduction in connectivity in schizophrenia has been documented in several imaging studies. A recent delayed match to sample study showed that reduced prefrontal cortex (BrA44) and right middle frontal cortex (BrA9 and BrA46) activation led to the failure to deactivate the inferior parietal lobe during encoding in patients (Anticevic, Repovs et al. 2013). On the other hand, activation of the prefrontal cortex, predicted the deactivation of the parietal regions in healthy controls (Anticevic, Repovs et al. 2013). The reduced patient group performance was correlated to the failure to deactivate the parietal network, and gave rise to maintenance deficits (Anticevic, Repovs et al. 2013). This suggests that the observed working memory deficits are partly due to the prefrontal cortex's inability to properly exert control on the parietal cortex in patients with schizophrenia. This result was also supported by an activation likelihood meta-analysis which included 15 studies of unaffected first-degree relative (Zhang, Picchioni et al. 2016). A reduced activation of the right inferior frontal gyrus (BrA44) and middle gyrus (BrA9) was observed, which was accompanied by an increased activation of the inferior parietal lobule (BrA40), and frontopolar (BrA10) cortex in first-degree relatives of patients with schizophrenia. As the uncoupling of prefrontal and parietal cortex was also observed in first-degree relatives, this suggests that the reduced prefrontal-parietal connectivity could be an underlying predisposition for schizophrenia. Furthermore, those two studies highlight the importance of the parietal cortex's deactivation by the prefrontal cortex during a complex working memory task. In fact, those regions are related to the default mode network (DMN) (Zhang, Picchioni et al. 2016). The DMN is the "resting state" of the brain, which is inhibited when cognitive demands are present (Abigail G. Garrity , Godfrey D. Pearlson et al. 2007). Simply put,

the DMN is involved in self-reflection, and to the internal and external attention of a stimulus (Abigail G. Garrity , Godfrey D. Pearlson et al. 2007). Therefore, in order to properly attend a task, the DNM needs to be deactivated, in order to redistribute the attentional capacity to the cognitive task (Abigail G. Garrity , Godfrey D. Pearlson et al. 2007). Following this logic, in addition the failure of properly focus attentional resources, patients would also fail to deactivate the regions that are not necessary to the task, further reducing their attentional capacity.

In summary, reduced coupling between the prefrontal and parietal cortex has been repeatedly reported in schizophrenia. This network seems to be crucial for most working memory tasks, and its alteration in schizophrenia could underlie the common working memory deficit. Indeed, alteration in this circuit could lead to various deficits. First, the inability to recruit the attentional network when the information is presented could result inappropriate target encoding, or increased distractibility. Moreover, failure to suppress default activity would inhibit memory formation contributing to encoding deficits (Anticevic, Repovs et al. 2013). Finally, the inability to focus on internal representations, which are stored in parietal regions, due to failure to inhibit the DMN and decreased attentional resources, could also contribute to the maintenance and manipulation deficit (Anticevic, Repovs et al. 2013). It is possible to investigate working memory in schizophrenia through a number of tasks and methodologies. One of those working memory function, which is called binding, relies on a number of processes that impaired in schizophrenia. In fact, binding processes can require processes such as selective attention, manipulation, and encoding strategies. Yet, very few binding studies have been conducted in schizophrenia. Therefore, binding will be presented below, and its study in schizophrenia will then be exposed.

4. Binding

Binding refers to the integration of various features from different sources in a unique and coherent representation. Individuals process different features individually, yet, we are able to see an object, including its shape, colour, and location as an integrated whole (Baddeley, Allen et al. 2010). Therefore, various features can be integrated into

objects, episodes, or scenes (Karlsen, Allen et al. 2010). In order to properly perceive the world, this integrating process, as well as its maintenance in working memory is crucial (Addis and McAndrews 2006). Moreover, binding is critical in order to perform a number of cognitive functions, and everyday life operations (Olsen, Moses et al. 2012). For example, it is important for autobiographical memory, as perception of an event can be bound as a whole, with its context, and then integrated into LTM (Baddeley, Allen et al. 2010). Creating those representations is thus essential for episodic memory (Mitchell, Johnson et al. 2000), and failure to create appropriate representations could lead to improper encoding and false memories (Lyle, Bloise et al. 2006).

In Baddeley's model, when information from the two "slave systems" need to be associated, binding can occur within the episodic buffer. Indeed, this compartment allows the visuospatial sketchpad and the phonological loop to interact. Therefore, information coming from different modalities, can be bound and integrated into coherent representations (Baddeley, Allen et al. 2011). As mentioned above, Baddeley and Cowan's models both suggest that four "chunks" of information can be temporarily held and manipulated in working memory (Cowan 2001). In fact, this capacity limit was observed in a study conducted by Luck and Vogel (1997). In that study, the authors created a visual working memory task in which participants had to either remember a change in colour, bar orientation, or had to monitor both. Individuals were able to maintain four integrated objects in working memory. Indeed, the authors observed that performances were equal for all conditions, hinting that objects were maintained in an integrated whole in memory (Luck and Vogel 1997). Moreover, the combined condition brought the memory span to up to eight features when there were four bars, as individuals were able to maintain the colour and orientation of each bar. In fact, participants could remember up to four features in simple objects, meaning that when four objects were maintained, up to sixteen features could be remembered. This thus implied that binding is an effective encoding strategy, as memory of integrated information was increased compared to single features, suggesting that binding optimizes memory (Luck and Vogel 1997, Addis and McAndrews 2006).

Finally, in Baddeley's model, the episodic buffer can be controlled by the central executive, but as mentioned, some observations hinted to the idea that the episodic buffer could also hold integrated information in a passive manner (Addis and McAndrews 2006, Luck, Danion et al. 2010, Grot, Petel Légaré et al. 2017). Passive binding implies that no voluntary effort is needed in order to create an association. For example, a binding study required participants to remember coloured shapes according to two conditions (Karlsen, Allen et al. 2010). In one condition (passive binding), participants were presented with an integrated image (e.g. red square). In the other condition (active binding) participants had to remember coloured shapes as well, but the colour and the shapes were spatially separated, and had to be unitized mentally. Therefore, both conditions required memory of an integrated whole consisting of the same number of characteristics (here, the form and the colour) (Karlsen, Allen et al. 2010). Yet, during the active binding condition, participants had to make a conscious effort to create an association between inputs. Active binding performance was generally lower, which suggested that this process might require more attentional processes than passive binding (Karlsen, Allen et al. 2010).

The study of binding in schizophrenia is important, as multiple processes are involved in this function. Depending on the condition, binding relies on various processes to a different degree such as selective attention, manipulation, encoding strategies. The study of this function in schizophrenia could thus dissociate various impaired processes. Moreover, inappropriate binding could result in false associations and inaccurate representations, which are typical in schizophrenia.

b) Binding in Schizophrenia

Several studies have considered binding in schizophrenia. For example, Burglen, Marczewski et al. (2004) found that patients with schizophrenia had a lower performance when remembering object-location combination compared to individual features. On the other hand, controls performed equally in both conditions, which led them to believe that a specific binding deficit was present (Burglen, Marczewski et al. 2004). Several studies support this finding, showing that patients have more difficulty remembering the combination of characteristics rather than individual features (Burglen, Marczewski et al. 2004, Salamé, Burglen et al. 2006, Giersch, van Assche et al. 2012). Conversely, others report no difference between binding performances and individual features (Gold, Wilk et

al. 2003, Luck, Foucher et al. 2008, Chhabra, Badcock et al. 2013). For example, Luck and colleagues (2010) found binding and single feature performance of schizophrenic patients did not significantly differ, which led the authors to hypothesize that there was no specific binding deficit in schizophrenia. This study goes in line with previous findings, in which there was no specific deficit in bound information compared to individual features in schizophrenia (Luck, Foucher et al. 2008, Luck, Buchy et al. 2009). To disentangle findings, a meta-analysis combining 10 binding studies in schizophrenia was conducted (Grot, Potvin et al. 2014). This study revealed that patient performance was equal for bound and discrete objects, but that both processes were lower in patients compared to controls (Grot, Potvin et al. 2014). Moreover, those deficits were present for all modalities (Grot, Potvin et al. 2014). Still, this meta-analysis only included studies using passive binding, which does not require conscious and voluntary effort.

On the other hand, a recent study of our laboratory observed that while passive binding was spared, active binding was impaired in patients with schizophrenia (Grot, Petel Légaré et al. 2017). Indeed, our previous study required participants to memorize three locations, and three words, which were either presented as unitized (passive binding), or were presented separately and required conscious effort to be bound (active binding). Patients did not have a deficit in passive binding, when the location and the word were already associated, supporting the meta-analysis results (Grot, Potvin et al. 2014). On the other hand, patient had a deficit in the active binding task, which required conscious effort (Grot, Petel Légaré et al. 2017). Those results therefore imply that patients with schizophrenia have a specific deficit in active binding, which could be due to the requirement of top-down regulation such as manipulation, attentional processes, and executive control. Indeed, this goes in line with the working memory literature, which states that patients have a maintenance deficit, which is exacerbated when manipulation is required (Kim, Glahn et al. 2004, Cannon, Glahn et al. 2005, Hao-Yang Tan, Wei-Chieh Choo et al. 2005). Moreover, as mentioned before, patients with schizophrenia have trouble finding optimal encoding strategies, and would therefore be deficient when the association between objects or words has to be voluntary. Passive binding, on the other hand, would be spared at is it is a bottom-up process, and would

require less higher order cognitive processes. This could thus underlie the discrepancies in the relational and associative field of schizophrenia.

All in all, the comparison between active and passive binding allows the dissociation of a specific deficit in patients. Those functions require the involvement of various regions, depending on their encoding demands, and the isolation those regions could reveal a specific impairment in schizophrenia. Therefore, the neural correlates of active and passive binding will be exposed below, followed by their involvement in schizophrenia.

c) Cerebral Regions Associated with Binding

Before presenting anatomical correlates of binding in schizophrenia patients, it is important to assess neural correlates of binding in healthy subjects.

First, the prefrontal-parietal network described previously has been linked to binding, which supports the hypothesis that it is involved in most working memory tasks (Rottschy, Langner et al. 2012). Indeed, numerous studies suggest that the posterior parietal cortex is involved in the maintenance of combined verbal-spatial information (Wu, Chen et al. 2007, Luck, Danion et al. 2010), and that the prefrontal cortex is involved to a greater extent when the inputs have to be reorganized voluntarily (Bor, Duncan et al. 2003, Campo, Poch et al. 2010). Moreover, Todd and Marois (2004) found that the posterior parietal cortex was important for encoding and temporary maintenance during visuospatial binding task (Todd and Marois 2004). In their study participants were shown a screen with coloured discs. After a delay, a target disc was presented, and participants had to determine whether it was identical in colour and in location to the previously shown disc. The activity of the posterior parietal cortex was correlated with the information storage capacity during the task (Todd and Marois 2004). The authors thereby suggested that the posterior parietal cortex could be responsible for the limited visuospatial information storage (Todd and Marois 2004). Furthermore, the parietal cortex has also been related to integrated phonological information maintenance. Indeed, Addis and colleagues (2006), showed an involvement of the parietal cortex in their verbal binding task which was hypothesized to be involved in semantic information storage. Their study also highlighted the role of the left prefrontal cortex during voluntary

associative encoding. Moreover, the authors also found an important negative relationship between prefrontal and parietal cortices, thought to represent the modulation of attention (Addis and McAndrews 2006).

Yet, as mentioned, various methodologies in working memory would recruit other areas. Accordingly, the medial temporal region seems to be involved in binding process specifically. Indeed, a number of neuroimaging studies support that binding is performed by the hippocampus. Activation of this region was reported when encoding word pairs (Meltzer and Constable 2005, Addis and McAndrews 2006), objects pairs (Achim and Lepage 2005), name-face pairs (Sperling, Chua et al. 2003) item-source (Davachi, Mitchell et al. 2003) and item-location (Sommer, Rose et al. 2005, Addis and McAndrews 2006, Olson, Moore et al. 2006, Piekema, Kessels et al. 2006, Finke, Braun et al. 2008, Hannula and Ranganath 2008). Furthermore, the location of the hippocampus puts it at an advantage to perform binding. Indeed, this structure receives inputs from a number of regions, such as the visual and auditory stream, as well as the temporal and parietal lobes (Olsen, Moses et al. 2012). This would enable the integration of a number of information coming from sensory and associative regions (Olsen, Moses et al. 2012)

Numerous studies support this idea. For example, Olson and colleagues (2006) conducted a study in which participants with hippocampal lesions were submitted to a visual binding task. Participants had to remember objects and their locations on a 3 x 3 matrix, and individuals with damaged hippocampus performed significantly worse when asked to remember combined object and location (Olson, Moore et al. 2006, Baddeley, Allen et al. 2010). Yet, as the hippocampus is important for spatial processing, there is still a debate on whether it is only necessary for tasks requiring binding of spatial information. Indeed, this distinction was proposed by Piekema, Kessels et al. (2006), as a delayed match-to-sample task activated the hippocampus for the maintenance of object-location task, but not for the object-colour combination or single features task. Still, a number of studies observed that the hippocampal formation was involved in verbal associations, and other non-spatial tasks (Meltzer and Constable 2005, Addis and McAndrews 2006). For example, Henke, Weber et al. (1999) found that the hippocampus was crucial for establishing new semantic associations, as new associations increased hippocampal activity.

Additionally, the medial temporal lobe seems to be involved in all temporal processes of binding. Hannula and Ranganath (2008) used a relational memory task where four objects were presented in different locations, with nine probable locations. Subjects had to maintain and mentally memorize the grid, and then identify if the right objects were in the correct location (Hannula and Ranganath 2008). This task thus required relational memory, as well as manipulation. Activation of the hippocampus during encoding and retrieval predicted success in the relational task (Hannula and Ranganath 2008). Moreover, the hippocampus was activated very early during encoding, a period when only regions involved in perception are normally activated (Riggs, Moses et al. 2009, Olsen, Moses et al. 2012). This suggests that the hippocampus is not only necessary for the maintenance of bound information, but also for it's encoding.

Furthermore, Olsen, Moses et al. (2012) argued that the hippocampus is necessary for both active and passive binding. Yet, the important difference is that prefrontal strategies would be necessary for optimal encoding during active binding (Addis and McAndrews 2006). Indeed, the prefrontal cortex would be required to create appropriate associations between stimuli, which could then be bound by the hippocampus (Lepage, Habib et al. 2000, Addis and McAndrews 2006). Supporting this, Addis and colleagues (2006) used a task in which semantic memory was assessed with words that either had associations between them (relational load), or that did not (generative load). The hypothesis was that areas activated during the unrelated words trials would be linked to the generation of associations, while the pre-associated words would activate areas related to the general binding process. Verbal relational encoding, and establishing associative strategies activated the bilateral inferior frontal gyrus, with a more important left hemisphere involvement (Addis and McAndrews 2006). This supports the hypothesis that the prefrontal cortex coordinates active associative encoding. Moreover, this activation was accompanied by the activation of the left hippocampus, which is hypothesized as lateralized due to the verbal nature of this task. All in all, this study supports the idea that the inferior frontal gyrus is necessary to consciously find the appropriate relationship between inputs, in order to coordinate the hippocampus to combine and maintain this association (Addis and McAndrews 2006). A few studies have

been conducted to determine the neural correlates of binding in schizophrenia. Those will be described below.

d) Regions Associated with Binding in Schizophrenia

The neural correlates of binding in schizophrenia have been investigated (Luck, Danion et al. 2010, Grot, Petel Légaré et al. 2017). The study by Luck, Danion et al. (2010) involved passive binding, and as mentioned before, there were no differences between binding and single feature memory, as patients performed below controls in both conditions. However, this study is interesting as it put forward the neural correlates of passive binding. In healthy controls, the hippocampus and parahippocampal gyrus were involved in encoding and maintenance of bound information (Luck, Danion et al. 2010). Conversely, patients showed an activation of the medial temporal regions during encoding, but not during maintenance, which points to a deficit in this phase. This study focused on passive binding, where cognitive demands are low (Luck, Danion et al. 2010). Therefore, this suggests that associative encoding by medial temporal region is spared when minimal encoding strategies are required. However, even if patients have no specific passive binding deficit, the maintenance of combined information in the hippocampus is still compromised, as they perform below controls. The authors also observed an increased activation of the inferior parietal lobule in both healthy controls and patients, hypothesized to be part of the rehearsal loop. Indeed, this region would be required maintaining attention towards internal representations (Luck, Danion et al. 2010). Nevertheless, this activation was not correlated to performance in the patient group, which was proposed to be due to non-specific mental effort (Luck, Danion et al. 2010). In short, this study showed that binding representations, even when successfully encoded, might have a decreased maintenance due to the hypoactivation of the medial temporal lobe, as well as aberrant parietal activation. This maintenance deficit leads to a reduced binding performance in patients with schizophrenia, but it is not enough to significantly differ from their individual features performance.

On the other hand, the recent study conducted by our laboratory explored the neural correlates of active binding in schizophrenia (Grot, Petel Légaré et al. 2017). As mentioned, a specific active binding deficit was observed in patients compared to controls, while passive binding was spared. A posterior parietal hypoactivation during

encoding was reported in patients. This could underlie a manipulation impairment (Grot, Petel Légaré et al. 2017). Indeed, manipulation is key in active binding, as features need to be actively combined in this condition (Grot, Petel Légaré et al. 2017). Therefore, it is possible that patients failed to properly organize the inputs into unified representations, resulting in an encoding deficit specifically in the active binding task. A reduced parietal activation during encoding could also result in selective attention impairment, a function required during the active binding task. Moreover, a hypoactivation of the ventrolateral prefrontal cortex was observed in patients during early maintenance. As mentioned, the VLPFC is part of the articulatory loop, and necessary for maintenance of verbal information (Rottschy, Langner et al. 2012, Grot, Petel Légaré et al. 2017). This region is also thought to maintain spatial and verbal information, and it is possible that failure to properly encode the association between the inputs resulted in decreased VLPFC activation.

In summary, as in all working memory tasks, binding requires the prefrontal-parietal network, which, as mentioned, has been documented as altered in schizophrenia (Karlsgodt, van Erp et al. 2008, Pérez-Iglesias, Tordesillas-Gutiérrez et al. 2010, Carletti, Woolley et al. 2012, Clemm von Hohenberg, Pasternak et al. 2014, Canu, Agosta et al. 2015). Modifications of the core network could therefore explain the deficit in active binding of patients. Yet, the medial temporal lobe, and as well its connection to the prefrontal cortex seems to be required for the binding processes specifically. In order to explain the alteration of functional activity, one can look at the anatomical findings in schizophrenia. Indeed, as mentioned, numerous anatomical alterations, in white and gray matter have been reported in schizophrenia (Goldman, Pezawas et al. 2009, Wheeler and Voineskos 2014). Moreover, changes in morphology in the prefrontal, parietal or the medial temporal lobe could explain the working memory deficit, as modifications of those regions could alter their functions (Guye, Parker et al. 2003, Greicius, Supekar et al. 2008, Bennett and Rypma 2013). The next section will thus explore possible alteration in the prefrontal, parietal, and medial temporal regions, as well as possible modification in the connection between those areas in schizophrenia. Indeed, a number of studies in schizophrenia indicate that the core network described by Rottschy, Langner et al. (2012), as well as the temporal medial-prefrontal network do not only show a gray

matter, but also a white matter alteration. This section will thus focus on gray and white matter changes in the prefrontal-parietal network, as well as the medial-temporal network, and explore its possible link with binding deficits.

5. Anatomical Alterations in Schizophrenia and Binding Deficits

a) The Prefrontal-Parietal Network Alterations in Schizophrenia

Gray Matter

Numerous studies report a reduction of thickness and density in the parietal and prefrontal cortex in patients (Thompson, Vidal et al. 2001, Whitford, Grieve et al. 2006, Schultz, Koch et al. 2010, Xiao, Lui et al. 2015).

Those reductions have also been documented in first-episode patients, at risk individuals, and unaffected first-degree relatives (Thompson, Vidal et al. 2001, Whitford, Grieve et al. 2006, Clemm von Hohenberg, Pasternak et al. 2014). This is interesting, as those populations have not been exposed to medication, which suggests that those alterations are present before onset, and are not due to medication side effects or disease chronicity. For instance, a longitudinal gray matter study with very early onset patients reported an important parietal lobe gray matter reduction in the first years, followed by a decrease in frontal gray matter, specifically of the DLPFC gray matter (Thompson, Vidal et al. 2001, Clemm von Hohenberg, Pasternak et al. 2014). Whitford and colleagues (2006) also found a reduction of prefrontal and parietal cortex gray matter in first episode patients. Furthermore, they observed an important decline in gray matter in the first 2 years especially in the parietal, the prefrontal and temporal region (Whitford, Grieve et al. 2006). This was replicated in a recent study with 128 medication naïve patients, who showed cortical thinning in the bilateral prefrontal and parietal cortex (Xiao, Lui et al. 2015). Finally, another first-episode patient study showed that there was cortical thinning in the frontal, DLPFC, temporal, and parietal regions (Narr, Bilder et al. 2005). These studies show that gray matter reductions in the prefrontal-parietal network are present at onset. Moreover, the longitudinal course seems to display an important decrease in thickness after onset.

Cortical thickness alteration of the prefrontal and parietal regions have also been linked to deficits in schizophrenia. Prefrontal cortical thinning was related to a diminution of executive functions, working memory, and attention in schizophrenia (Ehrlich, Brauns et al. 2012). Reduction of the parietal region gray matter was related to visuospatial and attentional deficits, as well as associative thinking impairments (Thompson, Vidal et al. 2001). Moreover, a disruption of the structure-function relationship was observed in patients. Indeed, while the lateral PFC cortical thickness was significantly associated with verbal recall and manipulation in controls, this correlation was not observed in patients (Ehrlich, Brauns et al. 2012). Conversely, verbal working memory was related to alternative areas in patients, such as the right middle and superior temporal lobe. Interestingly, as lateral prefrontal cortical thinning was observed in patients, this could suggest that changes in morphology led to the use of alternative networks (Ehrlich, Brauns et al. 2012).This goes in line with the disrupted structure-function hypothesis of schizophrenia (Hartberg, Lawyer et al. 2010). Finally, Wheeler, Chakravarty et al. (2014) also found that decreased DLPFC cortical thickness was associated with lower working memory performance in chronic and first-episode patients. Once again, as the same relationship is present in first-episode and chronic patients, it suggests that this could be an underlying pathology, and not simply caused by other factors such as duration of illness or medication.

White Matter

Modification of the prefrontal-parietal connectivity has been reported numerous times in schizophrenia (Collin, Kahn et al. 2014, Wheeler and Voineskos 2014). Indeed, imaging studies have shown that the connection between the prefrontal and parietal cortices is disrupted in patients (Petrides and Pandya 2002). Moreover, the fronto-parietal connection has been linked to verbal working memory in schizophrenia (Schneider, Habel et al. 2007, Karlsgodt, van Erp et al. 2008, Henseler, Falkai et al. 2010).

One of the most interesting fibres linking those two hubs is the superior longitudinal fasciculus (SLF). The SLF links the DLPFC and the middle frontal cortex with the parietal cortex (Petrides and Pandya 2002). Alteration of this fibre is one of the most consistent findings in ultra-risk patients, unaffected first-degree relatives, and

schizophrenia patients (Karlsgodt, van Erp et al. 2008, Pérez-Iglesias, Tordesillas-Gutiérrez et al. 2010, Carletti, Woolley et al. 2012, Clemm von Hohenberg, Pasternak et al. 2014, Canu, Agosta et al. 2015). This is relevant, as it suggests that SLF modification could occur before onset, irrespective of treatment, thus relating to the cause and not the consequence of the disease (Wheeler and Voineskos 2014). Finally, the left SLF is more consistently reported as reduced (Karlsgodt, van Erp et al. 2008, Sasamoto, Miyata et al. 2014).

Higher SLF FA values were correlated with better cognitive performances (Wassermann, Makris et al. 2016). For instance, a study by Karlsgodt, van Erp et al. (2008) showed that verbal working memory performance was correlated with the left, but not the right SLF FA in schizophrenia. The authors conclude that it is related to the verbal nature of the task, this modality being lateralized to the left. Moreover Baddeley (2007) proposed that the SLF, including the arcuate fasciculus are part of the working memory circuit (Baddeley 2007, Catani and de Schotten 2012). They proposed that the link between the parietal and frontal cortex could act as a memory trace rehearsal. This goes in line with the idea that the prefrontal cortex could direct the attentional focus to the appropriate internal or external information held in the parietal cortex (Catani and de Schotten 2012).

Another characteristic rendering the SLF study interesting in schizophrenia is its development. The SLF is the most vulnerable fibre during adolescence and early adulthood (Clemm von Hohenberg, Pasternak et al. 2014, Canu, Agosta et al. 2015). The prefrontal-parietal connection is one of the last to be myelinated, and develops until early adulthood (Clemm von Hohenberg, Pasternak et al. 2014, Lett, Voineskos et al. 2014). The end of this process corresponds to disease onset, which goes in line with the neurodevelopmental hypothesis of schizophrenia. Indeed, pruning and rearrangement of those axons occur at later stages (Canu, Agosta et al. 2015), suggesting that organization failure could trigger various symptoms. Moreover, myelination between the frontal and parietal lobe correlates with working memory capacity during development (Karlsgodt, Sun et al. 2008, Vestergaard, Madsen et al. 2011). Therefore, it is possible that this fibre is not properly reorganized during early adulthood, which could create deficits in the higher order cognitive functions needed to achieve complex tasks. This goes in line with

the fact that working memory deficits are present during the premorbid phase, can deteriorate at onset, and will stay stable through the disease. Indeed, the deterioration of those two regions, as well as their connection, occurs before onset, as well during the first years of the disease, which will then stabilize (Thompson, Vidal et al. 2001, Clemm von Hohenberg, Pasternak et al. 2014, Canu, Agosta et al. 2015). Thus, the prefrontal cortex develops last, and failure to establish proper connections during early adulthood with various regions could give rise to the disconnection hypothesis of schizophrenia.

Finally, another process occurring throughout development is the lateralization of this fibre. Indeed, hemispheric asymmetry is an important characteristic of the healthy brain (Catani and de Schotten 2012), and the SLF is unequally distributed between hemispheres (Catani, Allin et al. 2007, de Schotten, Dell'Acqua et al. 2011). The lateralization is independent of handedness (Vernooij, Smits et al. 2007), and develops until early adulthood, which also correlates with the onset of the disease. Moreover, the functional lateralization is correlated with the microstructural values, such as FA (Catani, Allin et al. 2007, Vernooij, Smits et al. 2007). Lateralization of the prefrontal-parietal network is related to various tasks. Correlations between the SLF lateralization and verbal memory task (Catani, Allin et al. 2007), as well as visuospatial task (de Schotten, Dell'Acqua et al. 2011) were observed in healthy subjects. Nonetheless, correlations between lateralization and performance are not straightforward, and seem to be quite heterogeneous throughout the population. Indeed, healthy subjects performed better when the SLF was lateralized to the right in a visuospatial task; yet, another study observed that the symmetrical arrangement of another part of the SLF provided an advantage in a verbal task (Catani, Allin et al. 2007, de Schotten, Dell'Acqua et al. 2011). Thus, the lateralization process is complex, but appears to be crucial for complex tasks (Catani, Allin et al. 2007, Catani and de Schotten 2012). Interestingly, a few studies reported that patients with schizophrenia have a lateralization alteration, which is either reduced, or even flipped in the parietal, and the frontal cortex gray matter, as well as in the white matter connecting them (Niznikiewicz, Donnino et al. 2000, Buchanan, Francis et al. 2004, Ribolsi, Daskalakis et al. 2014, Wheeler and Voineskos 2014). Furthermore, this aberrant lateralization was also observed at a functional level. Indeed, during a visuospatial working memory task, healthy controls activated the right fronto-parietal

circuit, consistent with the visuospatial specialization of the right hemisphere (Lee, Folley et al. 2008, Kim, Matthews et al. 2010). On the other hand, schizophrenia patients tended to have a bilateral activation of the fronto-parietal network, and the reduced asymmetry correlated with reduced performance, which implied a possible reduced specificity of circuits (Lee, Folley et al. 2008).

Thus, the prefrontal-parietal network seems to be altered both in the gray and white matter in patients. This network is required for most working memory tasks; yet, the network including the prefrontal and the medial temporal lobe seems to be important for binding specifically. Numerous studies report its anatomical modification.

b) The Prefrontal-Medial Temporal Network Alterations in Schizophrenia

Gray Matter

Feature binding relies heavily on the medial temporal lobe, and more specifically on the hippocampus. Interestingly, decreased hippocampal volumes is one of the most replicated finding in schizophrenia (Heckers 2001, Carol A. Tamminga 2010). This volume is usually reduced by about 5 %, a finding observed to a greater extent in the left hemisphere (Nelson, Saykin et al. 1998, Ian C. Wright, Sophia Rabe-Hesketh et al. 2000, John G. Csernansky, Lei Wang et al. 2002, Harrison 2004, Carol A. Tamminga 2010). Accordingly, reduced leftward asymmetry has also been reported in schizophrenia patients (John G. Csernansky, Lei Wang et al. 2002). In short, this would correspond to patients having a smaller left than right hippocampus (John G. Csernansky, Lei Wang et al. 2002). Smaller hippocampal size can be detected as soon as the first psychotic episode (Heckers 2001, Carol A. Tamminga 2010), and seems to decrease with disease progression (Chakos, Schobel et al. 2005). As this alteration is present before onset, it could contribute to the development of the disease. Indeed, it was observed that neonatal lesion of the ventral hippocampus in rats leads to schizophrenic symptoms in adulthood (Kevin Blot 2013). Therefore, hippocampal insult during neurodevelopment could lead to a number of schizophrenic symptoms.

As for cortical thickness studies, reduction of this value in the medial temporal region has also often been observed (Kuperberg, Broome et al. 2003, Ehrlich, Brauns et al. 2012, Sasamoto, Miyata et al. 2014). Indeed, a meta-analysis reported that the most common alterations in morphology were located in the medial temporal lobe (Ian C. Wright, Sophia Rabe-Hesketh et al. 2000). More specifically, a reduction of the hippocampus and the parahippocampal gyrus were the most consistent findings (Ian C. Wright, Sophia Rabe-Hesketh et al. 2000). Moreover, both schizophrenia patients and their first-degree relatives showed medial temporal lobe reduction (Karnik-Henry, Wang et al. 2012), suggesting a genetic contribution.

Changes in medial temporal lobe morphology also correlate with cognitive function. Patients with a hippocampal formation alteration, especially in the left hemisphere, have deficits in declarative memory tasks (Heckers, Rauch et al. 1998, Weiss, Schacter et al. 2003, Weiss, Zalesak et al. 2004). Moreover, a study combining 131 patients and 138 matched controls observed significant positive correlations between cognitive tasks and cortical thickness (Ehrlich, Brauns et al. 2012). A relationship between hippocampal volume and verbal learning and memory was observed. This relationship also applied to visual and logical learning (Sanfilipo, Lafargue et al. 2002, Ehrlich, Brauns et al. 2012). Episodic memory in relation to the medial temporal lobe was also studied in schizophrenia patients, their first degree relative, and well as controls (Karnik-Henry, Wang et al. 2012). The patients and their siblings had a reduced parahippocampal gyrus. Moreover, the authors observed that schizophrenic patients performed worse than any other group, and that unaffected siblings performed worse than controls. Importantly, there was a positive relationship between the parahippocampal volumes and performance, suggesting that this structure might contribute to the deficit (Karnik-Henry, Wang et al. 2012). Finally, another study showed that temporal cortical thickness was associated with verbal learning, processing, and executive function in healthy controls (Hartberg, Lawyer et al. 2010, Ehrlich, Brauns et al. 2012). Yet, schizophrenic patients had a more extended association, suggesting, once again an alteration of the structure-function relationship (Hartberg, Lawyer et al. 2010, Ehrlich, Brauns et al. 2012).

White Matter

As for the prefrontal-parietal connectivity, the prefrontal-temporal connectivity has also been often observed as decreased in schizophrenia. In fact, a recent meta-analysis including 407 patients and 383 controls found that the two most consistently affected regions were the left deep frontal and temporal white matter (Ellison-Wright and Bullmore 2009). Interestingly, neonatal lesion to the hippocampus is a prominent animal model of schizophrenia, and lesions to this region sometimes lead to DLPFC dysfunction (Meyer-Lindenberg, Olsen et al. 2005). Moreover, the connectivity between those two regions is associated with cognitive functions. Indeed, Wolf, Gur et al. (2007) found aberrant fronto-temporal connectivity during verbal encoding in patients. Greater connectivity between the temporal and DLPFC resulted in greater performance in controls. On the other hand, patients presented greater VLPFC-temporal connectivity, which the authors hypothesized to be related to ineffective compensatory strategies (Wolf, Gur et al. 2007).

The largest fibre track connecting the frontal and temporal lobe is the uncinate fasciculus (UF) (Ellison-Wright and Bullmore 2009). This white matter tract connects the temporal lobe with the ventral, medial and orbital part of the frontal lobe (Price, Cercignani et al. 2008, Catani and de Schotten 2012). Interestingly, a number of studies observed a reduced integrity of this fibre in schizophrenia (Burns, Job et al. 2003, McIntosh, Maniega et al. 2008, Price, Cercignani et al. 2008, Voineskos, Lobaugh et al. 2010, Hanlon, Houck et al. 2012). In fact, a decrease in the FA in the UF is one of the most frequent findings in chronic patients (Wheeler and Voineskos 2014). Moreover, reduction of this fibre has been reported in first-episode patients (Price, Cercignani et al. 2008), and unaffected relatives (Peters, Schmitz et al. 2009).

A reduced UF FA leads to a diminished functional connectivity between the medial temporal lobe and the prefrontal cortex, and the integrity of this fibre is linked to cognition (Kubicki, Westin et al. 2002, Burns, Job et al. 2003). Indeed, a reduced UF FA in patients has been linked to verbal memory, episodic memory, executive function, and working memory (Kelvin O. Lim , Babak A. Ardekani et al. 2006, Nestor, Kubicki et al. 2008, Spoletini, Cherubini et al. 2009, Henseler, Falkai et al. 2010, Hanlon, Houck et al. 2012). Importantly, a recent study tried to understand if the UF was necessary for the

transverse patterning task (Hanlon, Houck et al. 2012). This task relies on working and relational memory, and resembles binding. In short, transverse patterning task resembles the "rock paper scissors" game (Hanlon, Houck et al. 2012). In order to perform adequately, participants had to remember the correct relationship between 3 stimulus (Hanlon, Houck et al. 2012). Using "rock paper scissors" as an example; rock would win over paper, paper would win over scissors, and scissors would win over rock. Therefore, participants had to maintain the relationship between the stimulus, and manipulate which input would be appropriate depending on context (Hanlon, Houck et al. 2012). Another task used in this experiment was the visual hidden platform. In that task, participants had to use visual cues to discover a hidden platform. Both tasks are known to rely heavily on the DLPFC and the hippocampus (Hanlon, Houck et al. 2012). As the UF links the hippocampus and the DLFPC, the authors hypothesized that a reduced FA would compromise performance. Schizophrenic patients were heavily impaired in both tasks, confirming that this population has a dysfunctional relational memory (Hanlon, Houck et al. 2012). Moreover, patients had significant FA reduction in bilateral UF, and both working memory relational tasks were positively correlated to this value (Hanlon, Houck et al. 2012). Yet, there was no correlation with the UF in the control tasks, which were similar, but without the need of relational manipulation. This study thus put forward the importance of the UF during the voluntary manipulation of relational memory, and the requirement of the hippocampal and prefrontal cortex interaction. This could be applied to active binding, as in order to succeed in this task, the DLPFC would need to find the optimal strategy, and control the hippocampus. Indeed, the integration of new information and associations would rely on this interaction (Hanlon, Houck et al. 2012). This relationship would thus be key to create new, or be able to use old relationships, as well as manipulate them. Interestingly, reduction of hippocampal-prefrontal connectivity is correlated with positive symptoms (Henseler, Falkai et al. 2010). This could be explained by the fact that integration and association of new information could be compromised, which would create false perception and delusions (Henseler, Falkai et al. 2010).

The interaction between prefrontal and medial temporal region was also assessed in a study by Meyer-Lindenberg, Olsen et al. (2005). Using a functional connectivity

method and an N-back test, the authors found disturbed reciprocal connection between the DLPFC and the hippocampus in patients with schizophrenia. The authors also observed that the inferior parietal lobe and the DLPFC were negatively coupled with the hippocampus in healthy patients. When working memory load increased, healthy control had decreased functional connectivity between the hippocampus and the DLPFC. In patients, DLPFC activation and hippocampal deactivation were decreased, which led to task independent increased hippocampus activation. This could mean that the DLPFC does not modulate the hippocampus appropriately in schizophrenia, because of the relative independence of structure. This reduction of hippocampal modulation has since been replicated numerous times (Weiss, Goff et al. 2006, Ehrlich, Brauns et al. 2012).

Finally, Kubicki, Westin et al. (2002) found that healthy controls have a greater left than right UF, while patients did not have this lateralization. The possible reduced left lateralization has been found in a number of schizophrenia studies (Kubicki, Westin et al. 2002, Voineskos, Lobaugh et al. 2010). However, results are heterogeneous (Catani and de Schotten 2012, Olson, Heide et al. 2015). Indeed, a post-mortem study showed that the right UF is generally greater than the left in control subjects and that this relationship was maintained in schizophrenia (Highley, Walker et al. 2002). Therefore even though lateralization of this fibre has been documented, the direction of the lateralization is still under debate (Olson, Heide et al. 2015). Nevertheless, functional lateralization of this network was also observed. For instance, in the study by Hanlon, Houck et al. (2012), the verbal task activated left hippocampal formation while the non-verbal task activated the right hippocampal formation.

All in all, working memory depends on the tight coordination of various regions with the prefrontal cortex (Lett, Voineskos et al. 2014). Coupling between prefrontal and parietal cortex increases with memory load, manipulation demands, and is required most working memory tasks (Rottschy, Langner et al. 2012, Lett, Voineskos et al. 2014). On the other hand, the connection between the prefrontal cortex and the medial temporal lobe seems crucial for binding specifically. A number of studies show that patients with schizophrenia have a prefrontal dysconnectivity (Zhou, Fan et al. 2015), which could explain their broad deficit in a number of working memory tasks. Schizophrenia is thought be a neurodevelopmental disease in which the formation and regression of

synapses are dysfunctional. This could lead to a reduction of gray matter in key regions, but also to their diminished connectivity. Indeed, cortical thinning was related to white matter reduction, which suggests that reduction in those two anatomical values could be linked (Sasamoto, Miyata et al. 2014). Working memory is extremely complex, and the study of a specific deficit might shed light on the complex phenotype expressed by patients. Binding allows the study of a specific process using perception, manipulation, encoding strategies, associative memory, and attentional capacity. As patients are not impaired in passive binding, it allows the distinction between associative memory, and manipulation in associative memory. Therefore, studying the specific deficit of active binding in working memory could allow better understanding of the impact of dysconnectivity and anatomical modifications in schizophrenia.

Objectives

Our previous study showed that schizophrenic patients had a specific active binding deficit (Grot, Petel Légaré et al. 2017). This is important, as it highlighted the specific cognitive and executive control dysfunction in patients. Our previous study focused on functional activations, and proposed that altered activity in the patient group could be responsible for the specific active binding deficit. Therefore, our main goal is now to determine whether this specific active binding deficit could be a result of altered anatomy in schizophrenia. Indeed, binding is underpinned by three principal structures: the medial temporal lobe, the parietal lobe, and the prefrontal cortex. Both cortical thinning and reduced connectivity has been reported in those regions, and reductions of those values have been related to cognitive dysfunction. A number of studies suggest that schizophrenia is related to hypofrontality, as well as prefrontal dysconnectivity (William M. Perlstein 2001, Jae-Jin Kim, Jun Soo Kwon et al. 2003, Meyer-Lindenberg 2005, Fang, Wang et al. 2017). Furthermore, a deficit in active, but not passive binding, suggests a lack of prefrontal control. The prefrontal cortex is linked by the UF to the medial temporal region, and by the SLF to the parietal region. **As sparse cognitive and anatomical alterations are present in schizophrenic population, our goal is to determine if specific anatomical modifications are responsible for the specific active binding deficit in schizophrenia.**

Hypotheses

Two main networks would be involved in active binding specifically. First, the prefrontal-parietal network is related to attention, manipulation and storage of information. The prefrontal cortex would be required in order to find an appropriate encoding strategy, and interact with the parietal cortex in order to manipulate information (Owen, Evans et al. 1996, D'Esposito, Aguirre et al. 1998, Glahn, Kim et al. 2002, Veltman, Rombouts et al. 2003, Müller and Knight 2006, Rottschy, Langner et al. 2012, Park and Gooding 2014). On the other hand, prefrontal-parietal connections would be less important for the passive task performance. The SLF links the prefrontal and parietal cortex, and has been reported as altered in patients in many studies (Karlsgodt, van Erp et al. 2008, Pérez-Iglesias, Tordesillas-Gutiérrez et al. 2010, Carletti, Woolley et al. 2012, Clemm von Hohenberg, Pasternak et al. 2014, Canu, Agosta et al. 2015). **We thus expect a reduced SLF integrity in patients, which would be correlated to the active binding, but not the passive binding task performance. Moreover, as white matter integrity was shown to influence the cortical thickness of the region it links, we expect the reduced SLF integrity to be linked cortical thinning in the prefrontal and parietal regions in patients (Sasamoto, Miyata et al. 2014).**

On the other hand, the binding process itself is achieved by the medial temporal lobe. The prefrontal cortex interacts with the medial temporal lobe in order to create new associations. However, if the associations were already provided, the medial temporal lobe region would be able to properly maintain this association, and would thus rely to a lesser extent on prefrontal control. Therefore, a reduction of the connectivity of those regions would also create a specific active binding deficit. Interestingly, the UF links those two regions, and is often described as reduced in schizophrenia (Burns, Job et al. 2003, McIntosh, Maniega et al. 2008, Price, Cercignani et al. 2008, Voineskos, Lobaugh et al. 2010, Hanlon, Houck et al. 2012). **We thus expect reduced UF integrity in patients, which would be correlated to the active binding, but not the passive binding task performance. We also expect that reduced UF will be linked cortical thinning in the prefrontal and medial temporal lobe regions in patients.**

Finally, as schizophrenia is a neurodevelopmental disease, the lateralization process and hemispheric specialization occurring during development could also be related to this deficit. Indeed, lateralization is thought to be important, especially for visuospatial and verbal functions. Visuospatial processes are concentrated in the right hemisphere, while verbal functions are more distributed to the left (Toga and Thompson 2003). Even though the degree to which lateralization is needed is still debated, authors agree that it could be related to performance. As our task will involve both verbal and visuospatial information, an exploratory analysis will be performed to determine whether lateralization is linked to the specifically to the task. **We expect that the degree of lateralization of the gray and white matter in the prefrontal, parietal and medial temporal regions will be altered in patients, and that this alteration could be related to the task performance.**

Methodology

1. Participants

Stéphanie Grot, a student in our laboratory performed patient recruitment and scanning procedures. The selection criteria, as well as the task have been described in a recently published article (Grot, Petel Légaré et al. 2017), and will be exposed below.

a) Patient Recruitment

Twenty patients diagnosed by psychiatrists of the *Institut Universitaire de Santé Mentale de Montréal* (IUSMM) were recruited. They were all diagnosed with schizophrenia according to the DSM-IV-TR definition (APA 2013). Moreover, all patients were in a stable phase for at least one month at the time of the study. Patients were all on antipsychotic medication. Two were treated with typical antipsychotics, and eighteen were treated with atypical antipsychotics (Grot, Petel Légaré et al. 2017). As patients were treated with various antipsychotics, a chlorpromazine equivalent (mg per day) was calculated for all participants (Woods 2003). This calculation was performed in order to be able to verify if any significant results could be due to this confounding factor.

Internet publicity and posters were used to recruit 23 healthy controls. Healthy controls reported no neurological or psychiatric disorders history. Moreover, they did not have any relatives presenting those disorders either. As mentioned, cognitive and working memory symptoms are present as an intermediate phenotype in first-degree relatives (Heather M. Conklin, Clayton E. Curtis et al. 2000). Therefore, the absence of psychiatric familial history in healthy controls was crucial, in order to ensure that no controls had any intermediate cognitive deficiency.

A few more conditions were required in order to be included in the study:

- **To be able to speak French:** The task contains written words, and it would have been difficult to match French and English words. This is important as our task, which will be described in the next section, relies on the phonological loop.

- **The absence of substance abuse history:** Substance abuse is overrepresented in schizophrenia population (Tandon, Nasrallah et al. 2009). It was demonstrated that substance abuse leads to working memory impairments by reducing the use of appropriate strategies in order to attain a goal (Potvin, Pampoulova et al. 2008). Yet, others report no effect of substance abuse on cognition (McCleery, Addington et al. 2006), and some even propose that cognition would be better in substance users as it would require better social functioning (Joyal, Hallé et al. 2003). Nonetheless, a meta-analysis by Potvin, Joyal et al. (2008) showed that substance abuse does have an impact on cognitive function, which will depend on a number of factors such as age and preferred substance. Therefore, the absence of substance abuse was required, to limit its contradictory effects on cognitive measures.

- **To have no contraindication for scans:** Magnetic resonance imaging (MRI) scanning is based, as indicated by its name, on magnetic fields. Simply put, imaging is performed by applying an external magnetic field, which aligns the "spins", allowing measurement of the relaxation of hydrogen atoms. Therefore, the presence of metal in this scanner would not only create image artefacts, but could also harm the participants that have any metal present in the body. The participants therefore completed a questionnaire, in order to exclude any individuals who had metallic foreign bodies such as a pacemaker, hip replacement, or dental implants.

The ethical comity of *Regroupement de Neuroimagerie du Québec* approved this study. All individuals participated in this study voluntarily, signed the consenting form, and obtained a financial payment for their participation.

b) Clinical Evaluation

Patients underwent the positive and negative syndrome scale (PANSS) evaluation, which measures the severity of three different types of symptoms in schizophrenia (Kay, Flszbein et al. 1987). As mentioned, those categories are positive, negative, and general symptoms. Patients were rated from 1 to 7 on 30 manifestations, with one representing

the absence of symptoms. Thus, a high score corresponded to a greater impairment. The mean and standard average values are presented in Table I. Finally, the structured clinical interview for DSM disorder (SCID) version of the interview was performed by healthy subjects, to exclude the possibility that healthy controls presented impairments in those areas.

c) Intellectual Testing

To measure IQ, the Weschler Adult Intelligence Scale, 3rd edition (WAIS-III) was administered. It contains seven subtests, rendering it shorter than the original version, but still accurate (Pilgrim, Meyers et al. 1999). The subtests include similarity, arithmetic, picture completion, block design, digit span, and information, and digit symbol (Pilgrim, Meyers et al. 1999). It was developed to assess psychiatric populations (Pilgrim, Meyers et al. 1999, Christensen, Girard et al. 2007). As mentioned, patients have trouble focusing, and have low sustained attention. Therefore, this version permits the assessment of IQ, while limiting the time, and thereby the loss of attentional resources.

Eight controls and six patients were excluded of the study. Five participants were excluded because of aberrant segmentation and parcellation in the cortical thickness study. Four participants were excluded due to missing performance data. Four other participants were excluded due to poor T1 scan quality. Finally, two participants were excluded due to missing DWI scans. The remainder of patients and controls were matched for age, sex, handedness, years of education, parental socio-economic status, and IQ (See Table I).

Table I: *Socio-demographic and neuropsychological average values (standard deviation) of both groups*

	Controls	Patients	T-test	P-value
	n=15	n=14		
Age	33.47(8.33)	36.86 (6.94)	-1.15	0.54
Gender	10M/5F	9M/5F	0.019 [1]	0.89
Handedness	84.76(25.52)	75.75(51.47)	0.58	0.33
Years of Education	14.17(21.38) [2]	12.14(2.23)	1.96	0.46
Parental Socio-economic status	43.13(22.42)	50.43(15.47)	-1.00	0.33
IQ	105.60(9.92)	96.79(11.92)	2.09	0.65
PANSS, Negative symptoms	-	15.71(3.37)	-	-
PANSS, Positive symptoms	-	16.07(5.82)	-	-
PANSS, General Symptoms	-	34.21(4.71)	-	-
PANSS, Total	-	66 (8.63)	-	-
Years of illness	-	11.29 (7.13)	-	-
CPZ equivalent mg / day	-	353.14 (152.23)	-	-

n: number of participants; M: men; F:female

[1] Chi Square Test

[2] Missing data from two healthy controls.

2. Cognitive Task

The experimental task has been described before (Grot, Petel Légaré et al. 2017), and is represented in Figure 5. Before scanning procedures, participants had a 4-minute training, with 3 trials per condition in order to get familiarized with the task. The task consisted of 6 blocks of 15 trials, with each condition presented in 5 successive trials. In each trial, presentation of the stimuli lasted 3 seconds (encoding phase). The target display presented 3 words and 3 spatial locations represented by an ellipse. There was a possibility of 12 spatial locations, spread in the same manner as numbers on a clock. The words were coloured, and an identical colour ellipse represented their spatial positions. Participants were asked to remember the association between words and their respective spatial position. The encoding phase was followed by a 10-second maintenance phase during which there was a fixation cross. A white word was then presented in one of the 12 possible spatial locations for 5 seconds (retrieval phase), and participants had to determine whether this combination was presented previously or not. A word presented in the adequate spatial location, meaning that the association was presented during the encoding phase, would consist of a hit. On the other hand, an association composed of an inadequate word or an inadequate position would consist of a lure. Therefore, it was crucial for individuals to remember the words, the spatial location, as well as their appropriate association. Importantly, during the retrieval phase, a white target was used, as performance is based on capacity to remember spatial location and words, it was thus necessary to limit the reliance of colour recognition. Finally, a 10-second interval was allowed between trials.

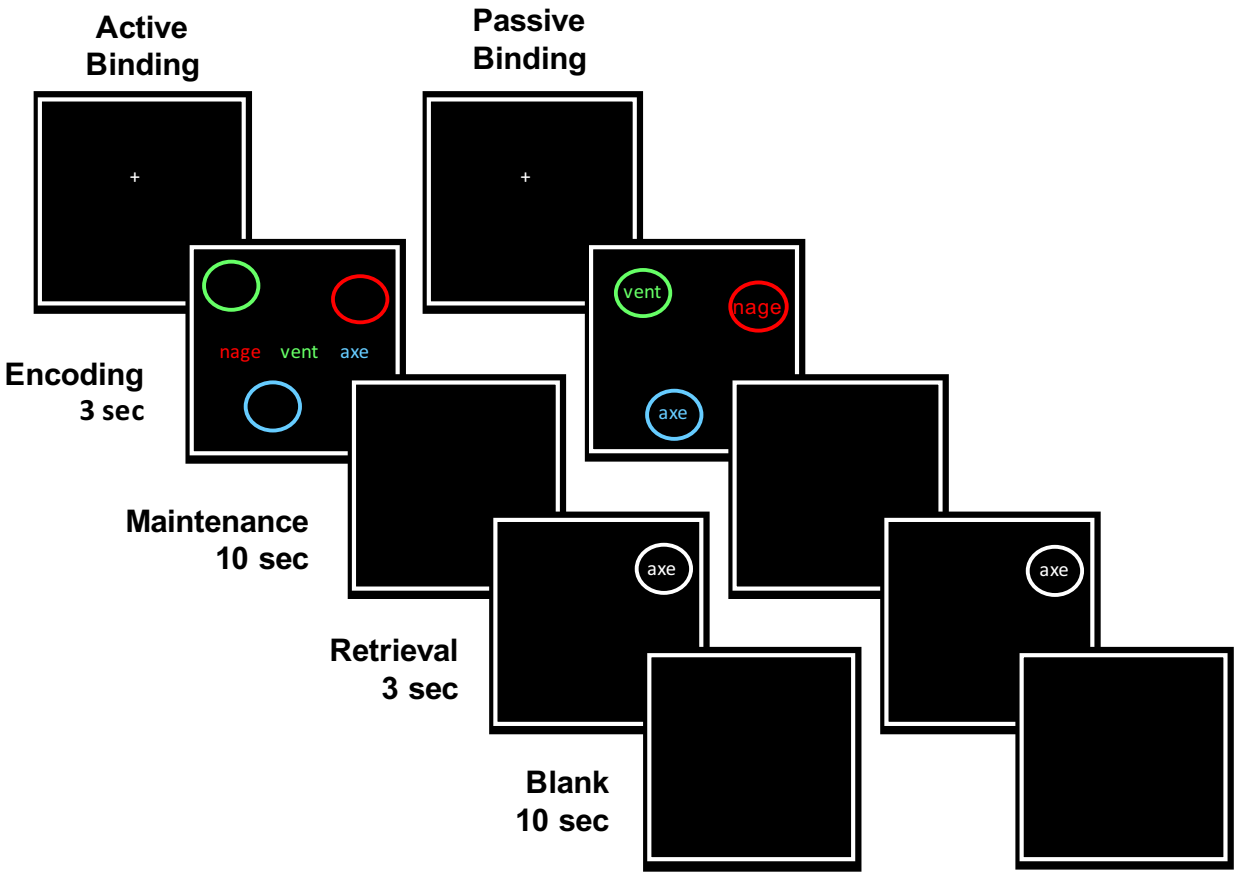
Participants were instructed to associate three words with three spatial locations according to two conditions. In the active condition, the words were centrally presented and were separated from the ellipses. Therefore, participants needed to mentally associate the words with their corresponding colour matching ellipse (e.g. green word would be associated with the green ellipse). On the other hand, in the passive condition, the three words and spatial locations were already associated (e.g. the red words would already be in the red ellipse). During retrieval, a white word was presented within a white ellipse, and participants needed to determine if this association was presented during encoding. Therefore, both the active and passive condition required the maintenance of the

association of the spatial and the verbal information. Yet, encoding differed, as the active binding condition would require adequate manipulation of information.

Verbal and visuospatial associations were used in order for the task to depend on the episodic buffer, as described by Baddeley's model. As mentioned before, both Baddeley and Cowan agree that one can hold about four "chunks" of information in working memory. Still, participants had to remember only three associations in order to limit the effect of reduced verbal and visual memory capacities in the patient population (Gold, Wilk et al. 2003, Luck and Vogel 2013). Moreover, the words were not semantically related, and chosen from a standardized list (Ferrand, New et al. 2010). For example, no phonologically analogous words were used, as similar sounding words are harder to remember (Baddeley 1966). Moreover the absence of semantic links was crucial as a meaningful list of words (e.g. sentence) is easier to remember (Baddeley 2010). All words were made up of two or three syllables, because as mentioned, word length has an influence on maintenance, with longer words reducing memory, due to decreased rehearsal capacity (Baddeley 2000). Furthermore, no emotional words were included, as the effect of emotional content on binding is controversial, some studies showing increased binding, while others showing decreased binding (Mather 2007). The task was presented by the E-prime software (version 2, Psychology Software Tools), and projected during the MRI scan.

Finally, the participants also performed another task. In that task, participants had to remember three words, and three spatial conditions, but did not have to remember their association. During the recognition task, a separate word and spatial position were presented, and participants had to determine if they were presented previously. This condition was part of the original fMRI study, as it included the same amount of information, but did not require their association. One could therefore imply which regions were linked to simple associative memory specifically, by contrasting the passive and separate condition. However, as mentioned, patients are mostly deficient executive, and manipulative processes, which is related to a prefrontal dysfunction. Moreover, as our current study is based on anatomical value, and we cannot infer which regions are activated during the separate task. Consequently, for the purpose of this study, we will use the passive binding condition as the control condition.

Figure 5: *Representation of the Active and Passive Binding Tasks Performed by the Participants*



3. Data Acquisition

Data acquisition was performed in two separate sessions. First the neuropsychological, demographic, and clinical values were acquired at the IUSSM or at the *Unité de Neuroimagerie Fonctionnelle* (UNF). Patients were tested on the values presented above by an IUSSM assistant. On the other hand, Stéphanie Grot performed the tests with healthy controls. The second sessions were conducted at UNF, where participants completed the behavioural task during fMRI scanning.

a) Scanning Procedures

Scanning was performed with an MRI Siemens 3 Tesla at UNF. After completion of the task T2, T1 and DWI were acquired. For the purpose of this study, only the two latter will be exposed.

T1 scans are 3D anatomical images. T1 scans were acquired with a 1x1x1 mm^3 resolution and 176 slices. An echo-planar (EP) sequence was used, with an Anterior>>Posterior (A>>P) encoding phase. The time of repetition was 22 ms, the time of echo was 9.20 ms, and the bandwidth was 1628 Hz/Px.

The DWIs were acquired with spin echo EP imaging in a 2x2x2 mm^3 resolution and 65 slices. Two b0 images (no diffusion gradient applied) were also obtained. Those were acquired with opposed encoding phase of A>>P and P>>A. Finally, a DWI was obtained with a b-value of 1000s/mm^2, and 64 directions, as well as one slice with no diffusion gradient. The b-value represents the strength and the timing of the gradients. A higher b-value will create more diffusion, but will decrease the signal to noise ratio. A 1000s/mm^2 b-value is often chosen for brain diffusion imaging (Kingsley and Monahan 2004, Descoteaux and Poupon 2012). Echo spacing for all DWI was 0.69 ms, with an EPI factor of 96, and a bandwidth of 1628 Hz/Px.

4. Anatomical Analysis

a) Diffusion-Weighted Imaging

Pre-processing

FSL (version 5.0.9) was used in order to minimize two main effects caused by echo-planar imaging: susceptibility-induced off-resonance field, and eddy currents (Woolrich, Jbabdi et al. 2009, Jenkinson, Beckmann et al. 2012).

First the susceptibility-induced off-resonance field was estimated, and then corrected by *top-up* (Andersson, Skare et al. 2003, Smith, Jenkinson et al. 2004). Susceptibility distortions usually happen at tissue junctions (e.g. between white and gray matter). Indeed, one of the problems arising in echo-planar images, is that distortions occur between tissues having different magnetic properties, which can then result in an altered diffusion tensor map (Andersson, Skare et al. 2003). One can correct those artefacts in pre-processing, as the same subject has more than one scan, and those susceptibility-induced field will be constant for the same subject. Therefore, it is possible to estimate those distortions, and correct them to obtain a non-distorted image. The susceptibility induced off-resonance field was thus estimated with the b0 images using the *top-up* command in FSL. The first b0 was extracted from our original diffusion-weighted data, and merged with the two b0 volumes acquired with negative-encode blips (A>>P) in the y direction, and positive-encode blips in the y direction (P>>A). This allowed us to have two distortions of identical magnitude, but in opposing directions (Andersson, Skare et al. 2003). By providing the acquisition parameters for all images, *top-up* was able to estimate the susceptibility-induced field. The encoding phase, the echo spacing (0.69 ms), as well as the EPI factor (96) was provided for each image. Susceptibility field estimation was accomplished by finding the volumes which will maximize the similarity between images, using the sum-of-squared difference between the image (Andersson, Skare et al. 2003). The estimation of the distorted magnetic field map was then applied to our original data in order to render an undistorted image. Moreover, *top-up* not only estimated the induced field, but also corrected possible subject movements during the acquisition. Indeed, as diffusion scanning is quite a long process, movement from the subject was almost unavoidable. All induced field maps files were

manually inspected. When there was inappropriate brain extraction, the mask was modified using the robust *BET* extraction tool in FSL (Smith 2002).

Second, eddy currents were corrected using the *eddy* tool (Andersson and Sotiropoulos 2016). When diffusion gradients are changing, local electric currents are generated. This phenomenon is called eddy current induced off-resonance field (Andersson and Sotiropoulos 2016). Those eddy current can then interfere with the gradients that are used for the spatial encoding (Jones and Cercignani 2010). This is a problem particularly in diffusion imaging, as the gradients are on for a very long time, which means that the rising and falling part of the gradients are separated in time, and cannot compensate for each other (Jones and Cercignani 2010). *Eddy* tool uses the *top-up* susceptibility distortion field map, as well as a non-distorted (b0) mask, separating brain from non-brain image, and corrects for the eddy currents. The acquisition parameters also need to be provided as well as the bvecs and the b-values. The bvecs values represent the vectors in the (x,y,z) planes of each direction acquired, while the b-values represent the gradient value applied in each direction (here 1000 s/mm^2). FSL pre-processing is advantageous, as *eddy* corrects the susceptibility distortion and the eddy currents, which means that there is only one DWI resampling (Andersson and Sotiropoulos 2016).

Deterministic Tractography

MedInria (version 2.2.3) (https://med.inria.fr/) was used in order to conduct deterministic tractography. The diffusion image corrected for eddy current and susceptibility-induced field was used, as well as the rotated bvecs. Those bvecs were used, as during pre-processing, the DWI was corrected for artefacts and movement, and corrected bvecs account for those changes (Jones and Cercignani 2010). The diffusion tensor field was estimated from the DWI and the bvecs. The fibres were reconstructed using tractography by extracting the preferred direction of water diffusion (principal eigenvalue) at each voxel, and a coloured FA scalar red-green-blue map was created.

In order to have an adequate tractography, a number of parameters were set. The diffusion tensors were extracted, voxel by voxels using the default 0.2 FA threshold, as it was shown as an optimal value to extract fibres (Taoka, Morikawa et al. 2009). Log-Euclidean metric method was used to smooth tensors (Toussaint, Souplet et al. 2007).

Smoothing value was set at 0.2, as it is the value used continuous fibre reconstruction (Thomas, Eyssen et al. 2005, Fillard, Pennec et al. 2007, Schlaug, Marchina et al. 2009). This value (from 0 to 1), determines how much the fibre can deviate from the tensor, and a higher value allows less deviation from the tensor (Toussaint, Souplet et al. 2007). Smoothing is important as it increases the signal-to-noise ratio, creating a normalized distribution data (Jones and Cercignani 2010). Finally, a minimum fibre length of 10 mm was required in order to be included in the reconstruction (Schlaug, Marchina et al. 2009).

All tracks were reconstructed manually by me, by using a two region of interest (ROI) method using the "AND" function. The ROIs for each fibre track are presented below. Only tracks passing by both ROIs were included. All tracks were then visually inspected to determine if they followed known anatomy. Out of place fibres were removed using the "bundling box" tool. The bundling box is a cube that can be moved and adjusted to any size, allowing the real time 3D cropping of fibres (Toussaint, Souplet et al. 2007). Therefore, outlier fibres were deleted using the bundling box, and the "ADD" button. Most of the deleted fibres were part of the corticospinal track, as well as fibres crossing to the opposite hemisphere. The FA values were extracted for each reconstructed fibre.

In order to control for possible bias, and validate the reproducibility of the ROI methodology, inter-rater and intra-rater reliability coefficients were calculated. Five random participants were selected, and all fibres were replicated 3 times by me. Intra-rater correlations were all greater than 0.8. To calculate inter-rater correlations, a second experimenter, Myrika Néron, also replicated all the fibres in those participants. All inter-rater correlations were greater than 0.8.

Finally, as an exploratory analysis, the laterality of each fibre was calculated using the formula below. This formula has been applied in many DWI studies (Powell, Parker et al. 2006, Vernooij, Smits et al. 2007, de Schotten, Dell'Acqua et al. 2011, Fernández-Miranda, Wang et al. 2015).

$$\textit{Laterality index (LI)} = (L-R)/(R+L)$$

Where L represents the left FA of the fibre, and R represents the right FA of the fibre. A positive value represents a left greater than right fibre. On the other hand, a negative value represents a right greater than left fibre. Moreover, a value of zero represents a symmetrical distribution of the fibre. FA values were used, as it was shown that the functional lateralization correlates with the fibres' microstructural arrangement (Powell, Parker et al. 2006, Vernooij, Smits et al. 2007, Catani and de Schotten 2012). The ROI methodology will be exposed below.

Uncinate Fasciculus: The methodology described by Wakana, Caprihan et al. (2007) was used. Coronal slice location was determined by the most posterior slice where the temporal and frontal lobe are separated (Wakana, Caprihan et al. 2007). In order to find this slice, the DWI image was used. Then, the FA scalar map was used to draw the ROI. The first ROI included the temporal lobe (Blue, Figure 6). The second ROI included the projection to the frontal lobe (Purple, Figure 6). This was performed for every patient, and for the left and right hemispheres. The left 3D reconstructed UF fibre is presented in Figure 7.

Figure 6: *ROIs Used to Reconstruct the Left Uncinate Fasciculus*

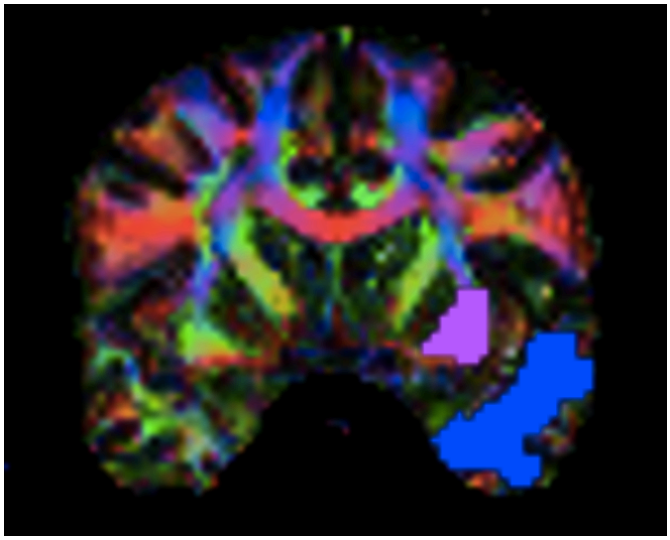
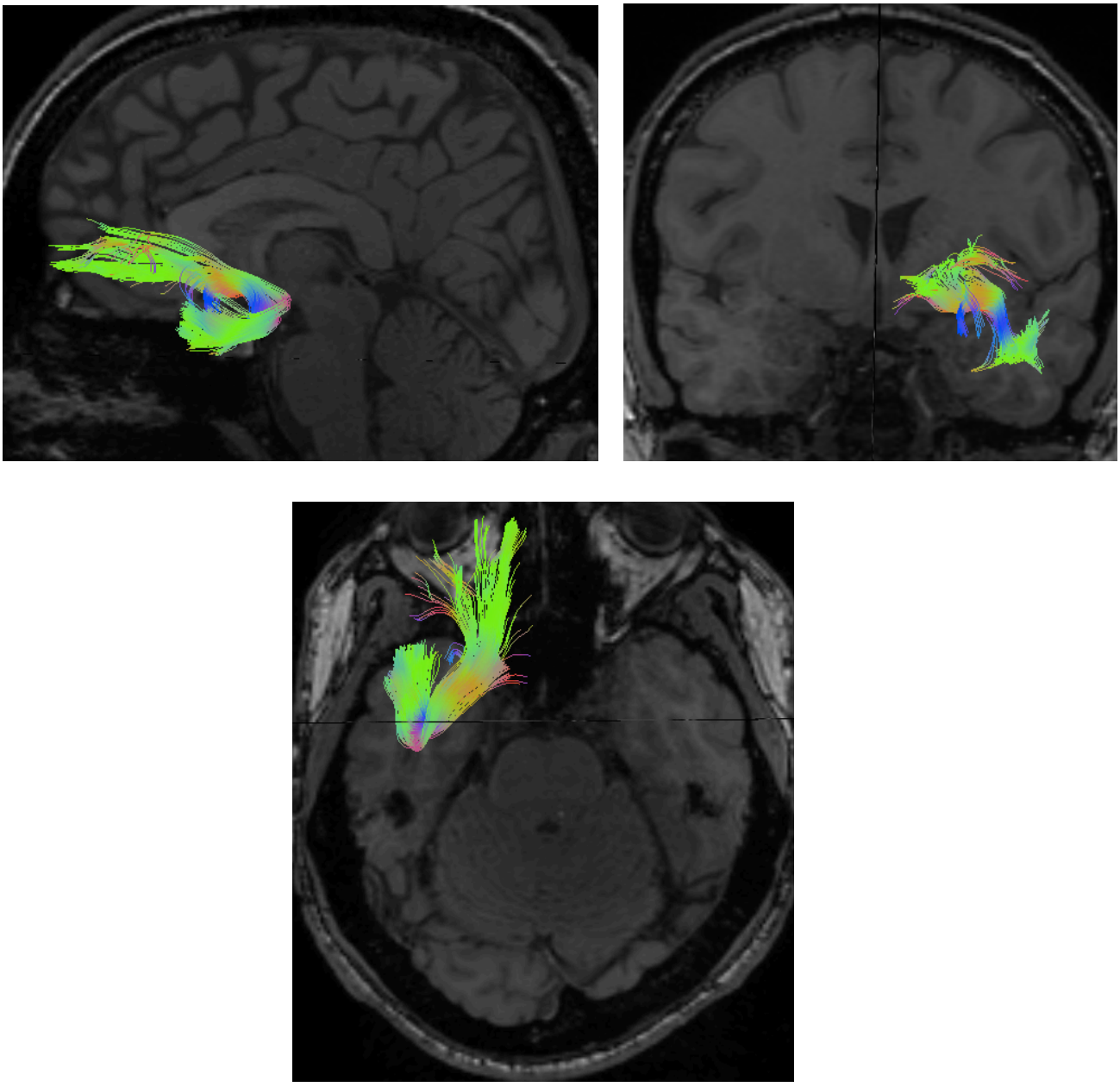


Figure 7: *Left Uncinate Fasciculus Reconstruction*



Superior Longitudinal Fasciculus (SLF): Before describing the methodology used for SLF reconstruction, it is important to comment on the differences in the literature regarding its construct. The SLF is thought to involve the fronto-parietal connections as mentioned, but some authors also include a temporal connection. This is represented by the arcuate fasciculus (AF) (Catani and de Schotten 2012). Furthermore, a number of publications use the words arcuate fasciculus and SLF interchangeably, yet it does not represent accurately the anatomy (Dejerine and Dejerine-Klumpke 1895, Catani and de Schotten 2012). Indeed, even if the arcuate is only a part of the SLF, their names are sometimes used as synonyms (Wassermann, Makris et al. 2016). This study will base itself on the definition of Makris, Kennedy et al. (2005), which separates the SLF in four components, the SLF I, SLF II, SLF III, and the arcuate fasciculus. We define the SLF as the frontal-parietal connection, which includes the arcuate fasciculus's temporal projections.

SLF: The ROI methodology used was previously described by Wakana, Caprihan et al. (2007). In order to determine the first ROI's location, the lowest axial slice in which the fornix could be identified was found, and the coronal slice was determined as the middle of the posterior limb of the internal capsule (Wakana, Caprihan et al. 2007). The green triangular shape represents the SLF, and the ROI encompassed it as well as its projections (Yellow, Figure 8). The second ROI involved finding the coronal slice that is at the splenium of the corpus callosum. The ROI is shown Figure 8 (Purple) (Wakana, Caprihan et al. 2007). The left 3D reconstructed SLF fibre is presented in Figure 9.

Figure 8: *ROIs Used to Reconstruct the Left SLF*

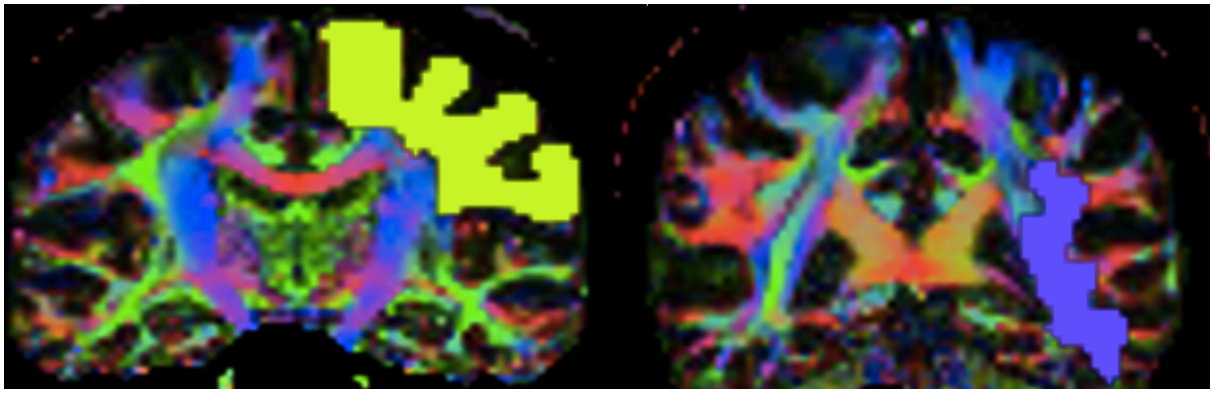
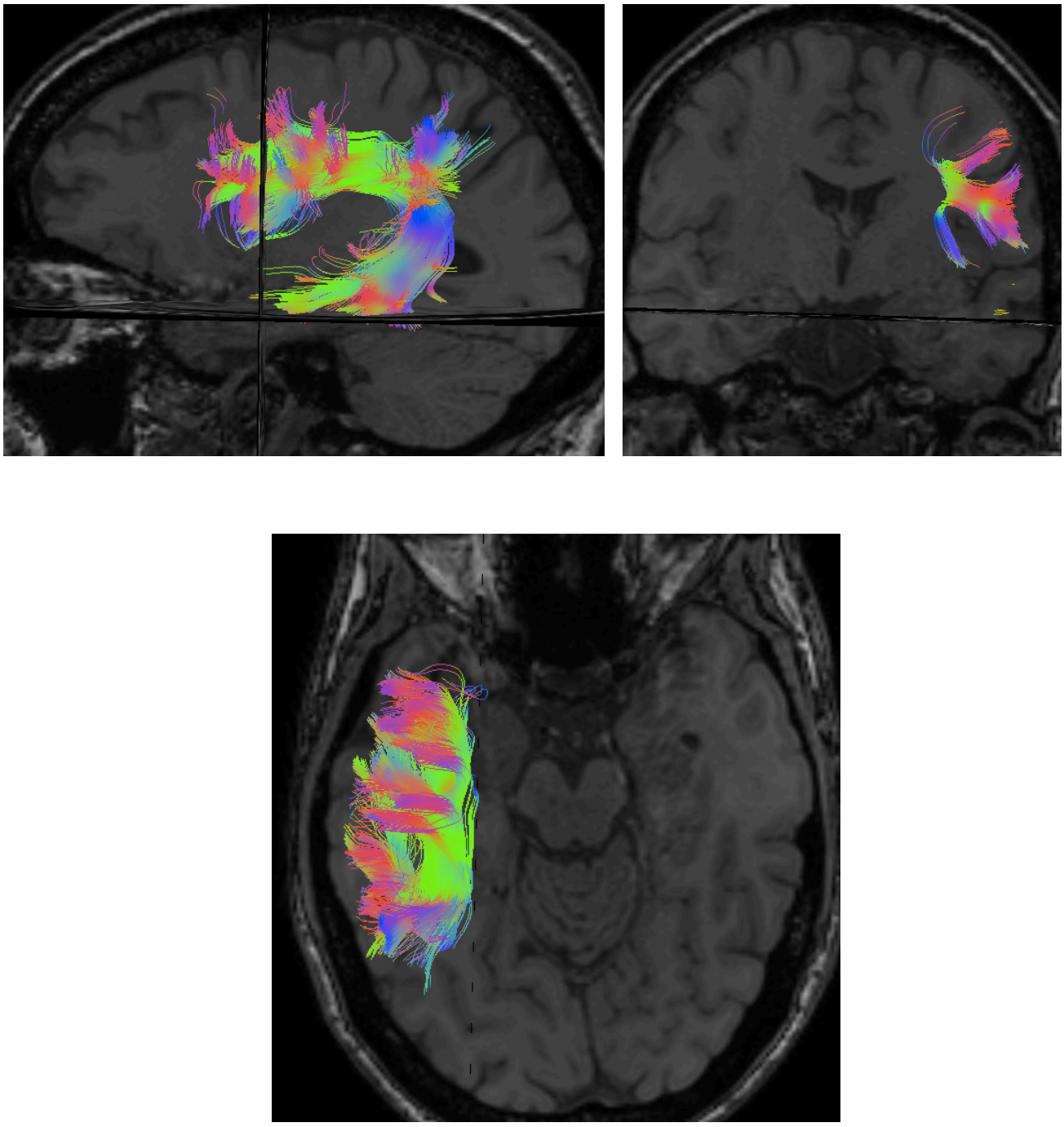
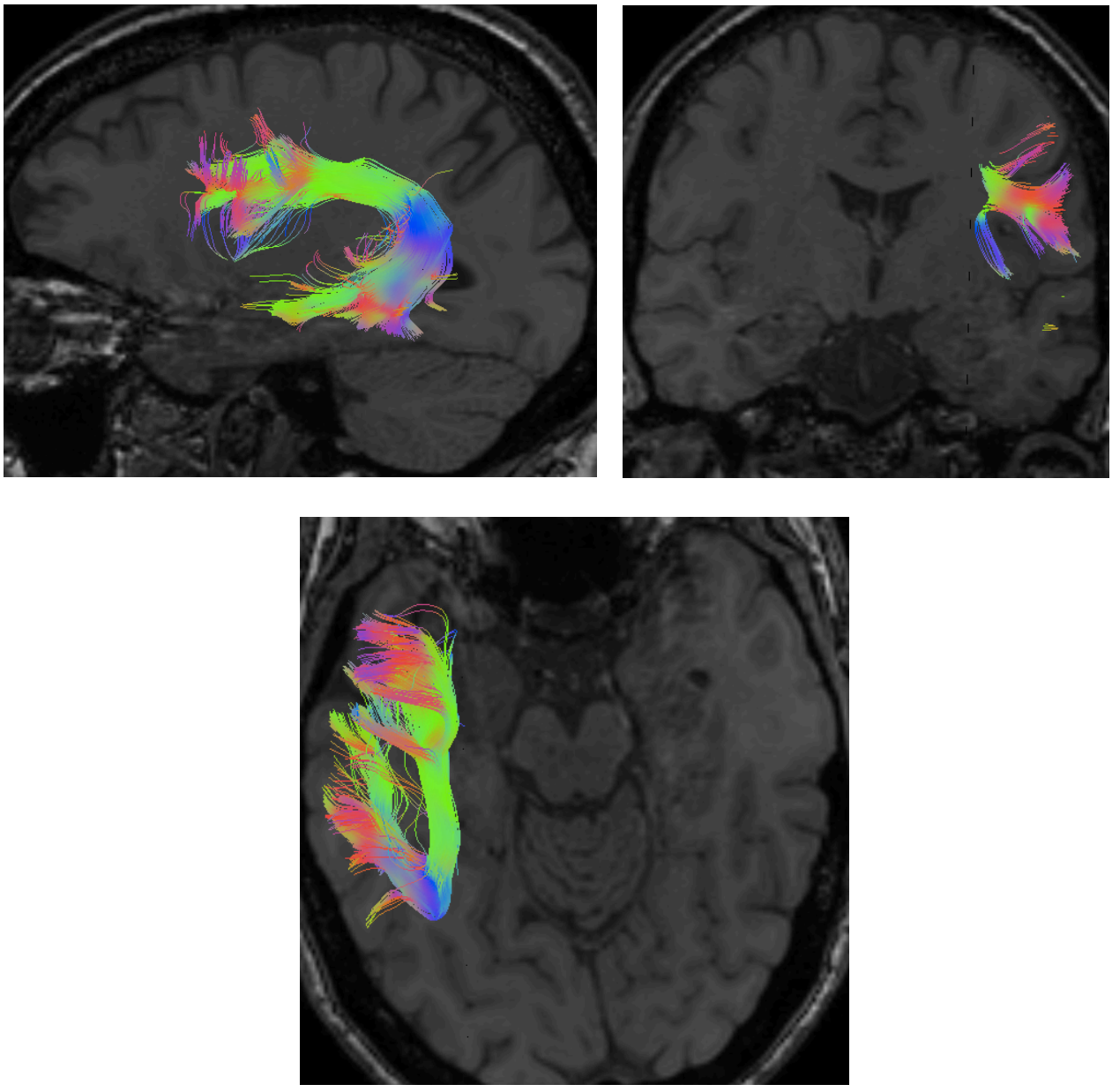


Figure 9: *Left SLF Reconstruction*



Arcuate Fasciculus: The AF connects the inferior frontal gyrus to the middle and posterior part of the superior temporal gyrus (Wassermann, Makris et al. 2016). Temporal projections were extracted by using the first SLF ROI, and by including only temporal projections using the bundling box. This analysis was added, in order to make sure that a possible effect is due to the frontal-parietal circuit, and not the temporal connection. The left 3D reconstructed arcuate fibre is presented in Figure 10.

Figure 10: *Left Arcuate Fasciculus Reconstruction*



SLF II: The frontal-parietal connection is composed of three fragments, SLF I, II, and III (Wassermann, Makris et al. 2016). The SLF II is of particular interest in this study as it connects the inferior parietal lobule to the lateral aspect of the superior, middle frontal gyrus, thereby connecting the parietal and dorsolateral prefrontal cortex (Catani and de Schotten 2012, Wassermann, Makris et al. 2016). The SLF II was extracted using the method described by de Schotten, Dell'Acqua et al. (2011). The first ROI was determined by selecting the middle frontal gyrus of the coronal slice at the anterior commissure (Yellow, Figure 11). The second ROI was determined by selecting the parietal lobe of the coronal slice at the posterior commissure (Red, Figure 11). All temporal projections were excluded. The left 3D reconstructed SLF II fibre is presented in Figure 12.

Figure 11: *ROIs Used to Reconstruct the Left SLF II*

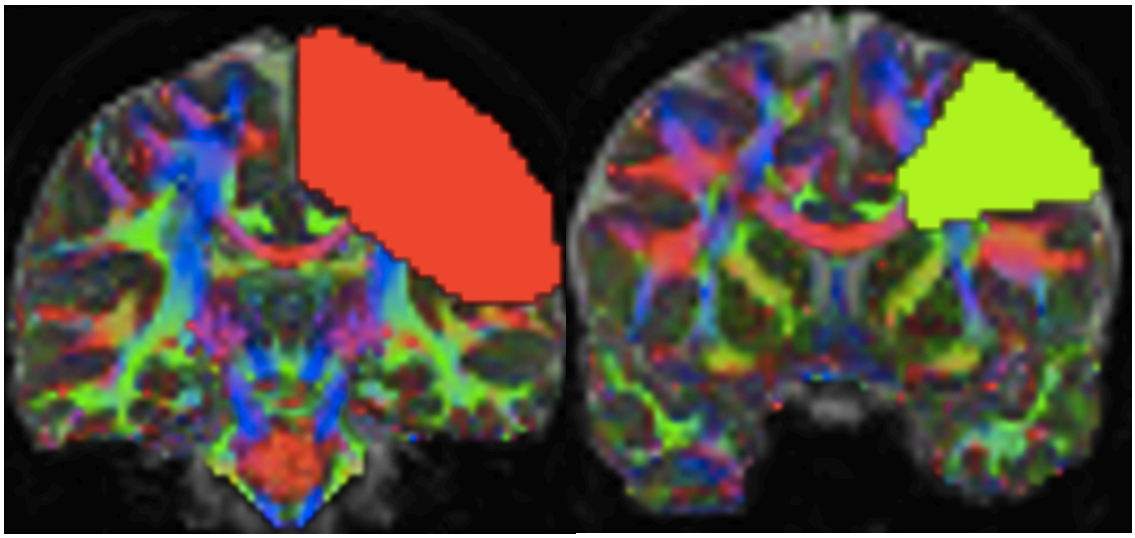
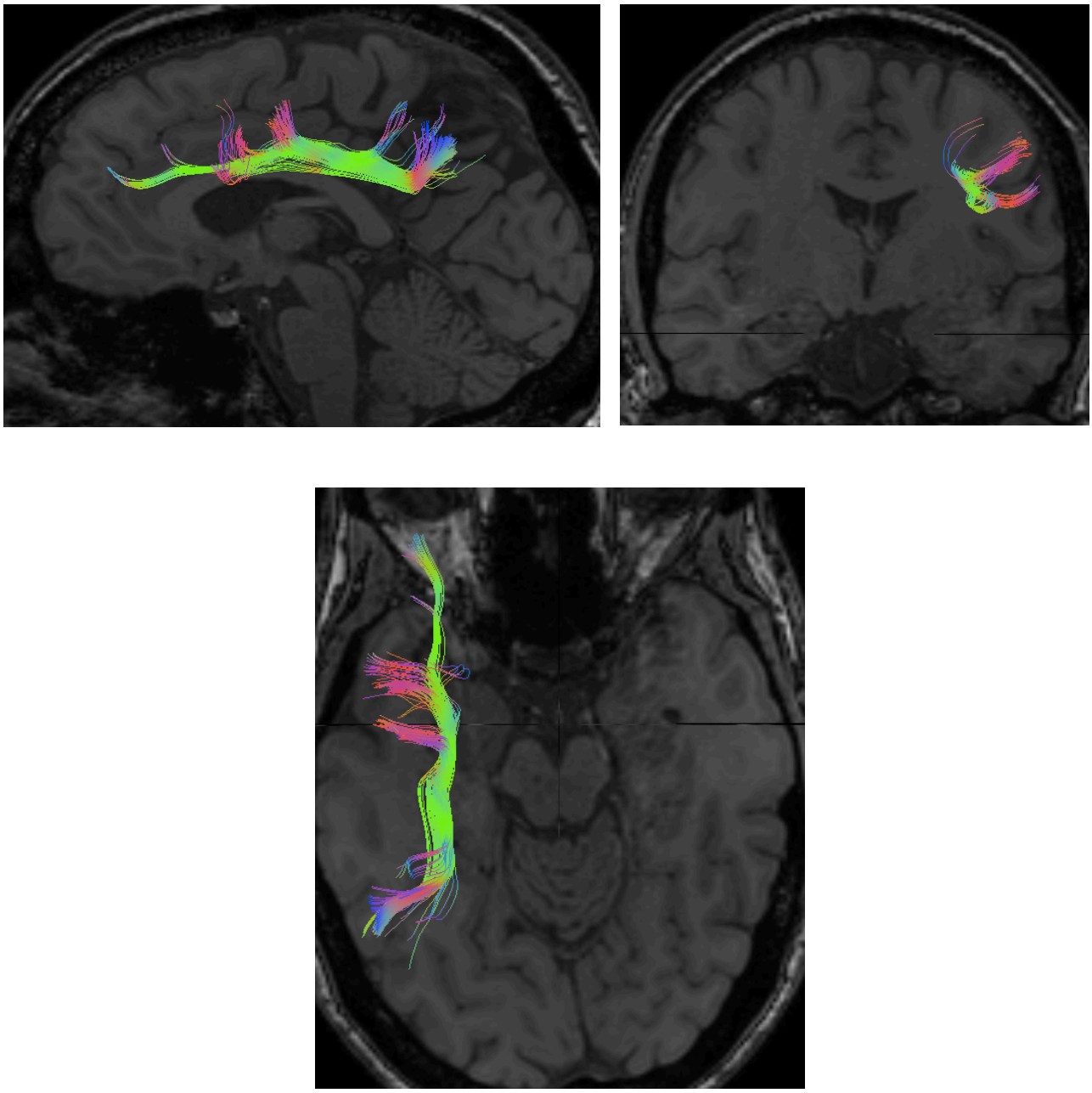


Figure 12*: Left SLF II Reconstruction*



b) Cortical Thickness Analysis

In order to determine whether white matter alterations correlated with cortical thickness alterations, a cortical thickness study was conducted. The T1 anatomical MRIs were submitted to CIVET, a fully automated pipeline (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET), in order to extract cortical thickness values. This protocol has been described previously (Zijdenbos AP 2002, Ad-Dab'bagh 2006). First, the T1 images were registered from a native to a standard stereotaxic space (MNI ICBM152 model) using a 9-parameter non-linear/affine registration, and corrected for signal intensity non-uniformities (N3 distance = 75) (Collins 1994, Sled, Zijdenbos et al. 1998, Fonov, Evans et al. 2009). Tissue classification of white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) was then computed (Zijdenbos, Forghani et al. 1998), accounting for partial volume effects (Tohka, Zijdenbos et al. 2004). Surfaces were extracted by computing boundaries between the GM and the WM (WM surface), and between the GM and the extra-cortical CSF (GM surface) for each hemisphere (MacDonald, Kabani et al. 2000, Kabani, Le Goualher et al. 2001, Kim, Singh et al. 2005). Each obtained surface was composed of 81,920 triangles and 40,962 vertices (Makowski, Bodnar et al. 2016). The cortical thickness maps were then extracted by estimating the distance in mm, between the WM and GM surfaces retransformed into their native space (Ad-Dab'bagh 2005, Lerch and Evans 2005). The cortical thickness maps were smoothed using a 30 mm kernel, as it has been shown to be the optimal level (Boucher, Whitesides et al. , Lerch and Evans 2005, Makowski, Bodnar et al. 2016).

Finally, as an exploratory measure, the asymmetry values of each vertex were also computed. As the same template is used for the registration of both left and right hemisphere, it is possible to assign each vertex to a corresponding one in the other hemisphere (Lyttelton, Karama et al. 2009). Therefore, from the plane x=0, each repositioned native vertex from the right hemisphere was subtracted from the repositioned native vertex of left hemisphere, in order to give a native space asymmetrical vector value (Lyttelton, Karama et al. 2009). Asymmetry was calculated for each native space vertex as the log-transformed ratio of left over right surface area (Lyttelton, Karama et al. 2009).

All scans were individually checked after being submitted to the quality control (QC) pipeline in order to determine if there were or aberrant cortical thickness or brain extraction, which lead to the exclusion of 4 healthy controls, and one patient due to inaccurate parcellation and brain extraction.

c) Statistical analysis

Performance

Statistical analysis was performed with Statistica 6.0 (http://www.statsoft.com/Products/STATISTICA/Product-Index). For cognitive task analysis, binding performance was estimated with the two-high threshold model (Snodgrass and Corwin 1988). This model estimates recognition performance by subtracting the false alarms (FAL)[3] from the hits (Pr = H-FAL). A hit refers to the accurate recognition of a target that was presented during the encoding phase (e.g. word in the appropriate spatial location). On the other hand, a false alarm refers to incorrect identification of a target that was not presented during the encoding phase (e.g. word in an inappropriate location). This model is useful as it allows the measurement of recognition capacities, while controlling for response bias (Snodgrass and Corwin 1988). Response bias is the tendency of participants to favour a response over another (Macmillan and Creelman 1990). For example, when individuals were asked if the association was presented during encoding, participants could have favoured the "yes" answer over the "no" answer, leading to a response bias. Therefore, the Pr value was calculated for each participant in each condition.

Task performance difference between groups was then calculated using repeated measures analysis of variance (ANOVA). Binding conditions (passive and active binding) were used as within-group factors, while groups were used as between-group condition (schizophrenic patients, healthy controls). The sphericity assumption was checked for all conditions. Newman-Keuls (NK) tests were used for *Post hoc* tests when necessary. Finally, the modified FDR method described by Narum (2006) was used to control for multiple comparison.

[3] FAL is used in order to avoid confusion with the abbreviation of fractional anisotropy (FA)

Finally, passive binding (Bp) was subtracted from active binding (Ba) in order to extract a value (BaBp). This value is thought to represent the executive and manipulation function, as binding is subtracted leaving the "active" part of the task. According to our hypothesis this value would represent the key function in which the patients are impaired.

Diffusion Tensor Imaging

FA values were extracted from the four fibres presented above. Repeated-measures ANOVA were used in order to calculate group differences. Lateralization conditions (left and right FA) were used as within-group factors, while groups were used as between-group condition (schizophrenic patients, healthy controls). Pearson correlations between tasks (Ba, Bp, BaBp) and FA values by groups were calculated. The BaBp contrast was considered as a separate analysis for the multiple comparison corrections, as it represents a process that is part of active binding.

Finally, an exploratory analysis was performed to determine if the lateralization of the fibres is altered in patients. A one-way ANOVA was used for group differences. Pearson correlations by groups were used to determine if there is a link between the performances and the lateralization index.

Cortical Thickness Analysis

Cortical thickness group differences were computed with MATLAB SurfStat toolbox (http://www.math. mcgill.ca/keith/surfstat). A general linear model was created using $Y = 1 + Group$, and tested in the contrast controls>patients and controls<patients. No other covariates were added as groups were matched. This resulted in a t-map, and possible significant clusters and peaks were extracted using the corrected threshold, random field theory (RFT), with an alpha value of 0.05. Results were projected onto a high-resolution average surface, with midline mask excluding the cerebellum and the brain stem.

Moreover, an exploratory analysis using the same general linear model was performed to detect asymmetrical group differences. As for cortical thickness values,

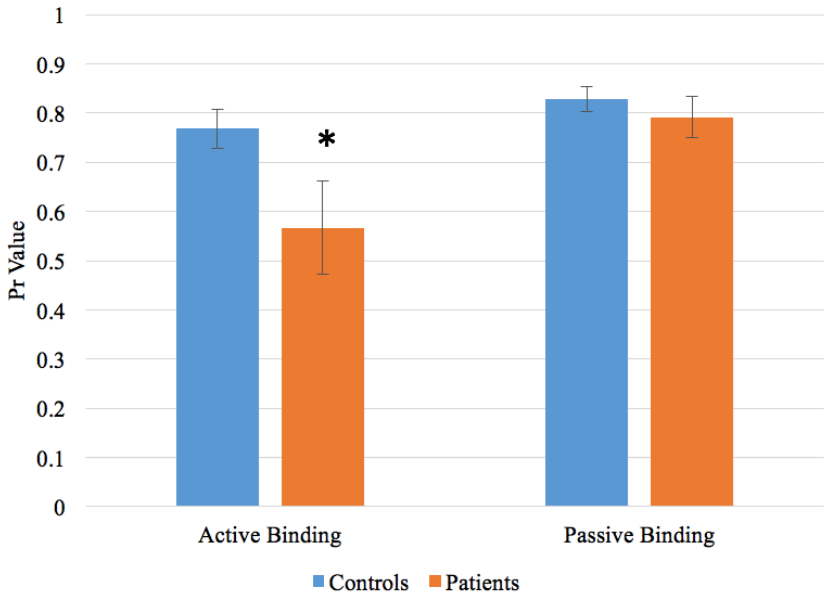
some variables have an effect on asymmetry, such as handedness and gender (Lyttelton, Karama et al. 2009), yet it was not controlled for in the model as groups are matched**.** Finally, the highest t-value of significant clusters was located in the contrast control> patients. A 10 mm radius ROI was extracted. Finally, this value was correlated to fibres, as well as the binding tasks.

Results

1. Binding Performance

The analyses revealed no significant group effect ($F(1,27) = 2.69$, $p = 0.11$, $\eta^2 = 0.09$), but a significant condition effect ($F(1,27) = 14.32$, $p = 0.001$, $\eta^2 = 0.35$), with lower performance for the active binding condition relative to the passive binding condition. More importantly, the interaction Group x Condition was significant ($F(1,27) = 4.74$, $p = 0.038$, $\eta^2 = 0.14$). NK *post hoc* tests showed that patients perform significantly worse on the active compared to the passive binding task ($p = 0.008$), unlike controls who performed equally for both binding conditions ($p = 0.50$). In addition, while the two groups exhibited equal performance for the passive binding condition ($p = 0.65$), patients performed significantly worse than controls for the active binding condition ($p = 0.02$).

Figure 13: *Performance (Pr value) by Group for the Active and Passive Binding Condition*



Behavioural performance for both groups is shown with the mean Pr (H-FL). The asterisk (*) illustrates significant group differences ($p = 0.02$), while the error bars represent standard errors.

2. Diffusion-Weighted Imaging Results

The FA average values of all isolated fibres, as well as their standard deviations are presented in Supplementary Table I. Moreover, the LI average values of all isolated fibres as well as their standard deviations are presented in Supplementary Table II.

a) Whole fibres:

Uncinate Fasciculus

Group comparison for both hemispheres: Repeated-measures ANOVA showed no group effect ($F(1,27)=0.865$; $p=0.36$; $\eta^2=0.03$). Yet, a laterality effect was observed ($F(1,27)=9,165$; $p=0,005$; $\eta^2=0.25$), with the left UF significantly smaller than the right UF in patients ($p=0.01$), while it was equal in controls ($p=0.51$). Finally, the interaction Group X Laterality was not significant ($F(1,27)=2.10$; $p=0.16$; $\eta^{2=}$ 0.07).

Pearson Correlations: No significant correlations were found between the tasks and bilateral UF FA in both groups (all $p>0.05$, after correction) (see Tables II and III).

Superior Longitudinal Fasciculus

Group comparison for both hemispheres: Repeated-measures ANOVA showed no group effect ($F(1,27)=2.41$; $p=0.13$; $\eta^2=$ 0.08), or laterality effect ($F(1,27)=2.18$; $p=0.15$; $\eta^2=0.08$). Finally, the interaction Group X Laterality was not significant ($F(1,27)=0.32$ $p=0.57$; $\eta^2=0.012$).

Pearson Correlations: No significant correlations were found between the tasks and bilateral SLF FA in both groups (all $p>0.05$, after correction) (see Tables II and III).

Table II*: Pearson Correlations Between the Tasks Performances and the FA Values of the UF and SLF Fibres*

	Controls		Patients	
	Passive Binding	**Active Binding**	**Passive Binding**	**Active Binding**
Left UF FA	r=0.29, p=0.30	r=0.38, p=0.17	r=0.41, p=0.14	r=0.30, p=0.27
Right UF FA	r=0.61, p=0.02	r=3.37, p=0.18	r=0.48, p=0.08	r=0.32, p=0.27
Left SLF FA	r=-0.25, p=0.38	r=-0.24, p=0.39	r=0.42, p=0.13	r=0.37, p=0.19
Right SLF FA	r=0.03, p=0.90	r=0.10, p=0.73	r=0.07, p=0.81	r=-0.22, p=0.44

Table III: *Correlations Between the BaBp contrast and the FA Values of the UF and SLF Fibres*

	Controls	Patients
	BaBp Contrast	**BaBp Contrast**
Left UF FA	r=0.08, p=0.78	r=0.16, p=0.58
Right UF FA	r=-0.02, p=0.93	r=0.14, p=0.63
Left SLF FA	r=-0.13, p=0.63	r=0.25, p=0.39
Right SLF FA	r=0.12, p=0.68	r=-0.35, p=0.23

Exploratory Analysis: Laterality index

Group comparison: One-way ANOVA showed no group difference for the UF LI ($F(1,27)= 2.14$; $p=0.16$; $\eta^2=0.07$), and the SLF LI ($F(1,27)=0.35$; $p=0.56$; $\eta^2=0.01$)

Pearson Correlations: No significant correlations were found between the UF LI and all tasks for both groups (all $p> 0.05$, corrected). A significant positive correlation was observed between the BaBp condition and the SLF LI in the patient group ($r=0.63$, $p=0.015$, corrected), but not in the active binding condition ($r=0.60$; $p=0.024$, corrected)[4]. Conversely, no significant correlations were found between the active binding performance, or the BaBp condition, and the SLF LI in the control group (all $p>0.05$, after correction). Finally, no correlations between the SLF LI and the passive task were observed in both groups (all $p>0.05$, after correction) (Table IV and V).

Table IV: *Pearson Correlations Between the Tasks Performances and the LI Values of the UF and SLF Fibres*

	Controls		Patients	
	Passive Binding	**Active Binding**	**Passive Binding**	**Active Binding**
LI UF	r=-0.32, p=0.24	r=-0.14, p=0.62	r=-0.13, p=0.66	r=-0.43, p=0.89
LI SLF	r=-0.36, p=0.19	r=-0.43, p=0.11	r=0.29, p=0.31	r=0.60, p=0.02

Table V: *Pearson Correlations Between the BaBp contrast and the LI Values of the UF and SLF Fibres*

	Controls	Patients
	BaBp Contrast	**BaBp Contrast**
LI UF	r=0.96, p=0.74	r=0.02, p=0.95
LI SLF	r=-0.32, p=0.25	**r=0.63, p=0.02***

* Significant correlations corrected FDR

[4] Three decimals are shown for the p-value instead of two for both Ba and BaBp task to demonstrate why BaBp is significative, but not Ba

b) SLF Subcomponents

As the SLF is comprised of both temporal and parietal connections, an analysis was conducted to determine if the possible observed effects were due parietal or temporal connections.

SLF II:

Group comparison for both hemispheres: Repeated measures ANOVA showed no group effect ($F(1,27)=1.76$; $p=0.20$; $\eta^2=0.06$), or laterality effect ($F(1,27)=2.80$; $p=0.11$; $\eta^2=0.09$). Finally, the interaction Group X Laterality was also non-significant ($F(1,27)= 0.46$ $p=0.50$, $\eta^2=0.02$).

Pearson Correlations: No significant correlations were observed, in both groups, between all task performances and the SLF II FA of both hemispheres (all $p>0.05$, after correction) (see Tables VI and VII).

Arcuate Fasciculus:

Group comparison for both hemispheres: Repeated-measures ANOVA showed no group effect ($F(1,27)=0.66$; $p=0.42$; $\eta^2=0.02$), or Laterality effect ($F(1,27)=3.68$, $p=0.07$; $\eta^2= 0.12$). Finally, the interaction Group X Laterality was not significant ($F(1,27)= 0.221$ $p=0.642$; $\eta^2= 0.01$).

Pearson Correlations: No significant correlations were observed, in both groups, between all task performances and the arcuate fasciculus FA of both hemispheres (all $p>0.05$ after correction) (See Table VI and VII).

Table VI: *Pearson Correlations Between the Tasks Performances and the FA Values of the SLF II and Arcuate Fibres*

	Controls		Patients	
	Passive Binding	**Active Binding**	**Passive Binding**	**Active Binding**
Left SLF II FA	r=-0.46, p=0.08	r=-0.12, p=0.67	r=0.13, p=0.65	r=0.46, p=0.09
Right SLF II FA	r=0.21, p=0.45	r=0.03, p=0.92	r=-0.22, p=0.45	r=-0.31, p=0.27
Left Arcuate FA	r=-0.24, p=0.39	r=-0.35, p=0.20	r=0.50, p=0.07	r=0.34, p=0.23
Right Arcuate FA	r=-0.21, p=0.47	r=-0.19, p=0.50	r=0.35 p=0.22	r=0.24, p=0.40

Table VII: *Pearson Correlations Between the BaBp contrast and the FA Values of the SLF II and Arcuate Fibres*

	Controls	Patients
	BaBp Contrast	**BaBp Contrast**
Left SLF II FA	r=0.26, p=0.36	r=0.54, p=0.05
Right SLF II FA	r=0.24, p=0.38	r=-0.29, p=0.31
Left Arcuate FA	r=-0.31, p=0.26	r=0.17, p=0.57
Right Arcuate FA	r=0.09, p=0.74	r=-0.09, p=0.76

Exploratory Analysis, Laterality index:

Finally, as the SLF leftward asymmetry is related to the executive aspect of the task (BaBp) in patients, LI subcomponents were also computed. This was performed in order to determine which part of the fibre is responsible for the observed correlation.

Group comparison: One-way ANOVA showed no group difference between the SLF II LI ($F(1,27)= 0.43$, $p=0.52$; $\eta^2 =0.02$), and the arcuate fasciculus LI ($F(1,27)=-0.55$; $p=0.47$; $\eta^2= 0.02$)

Pearson Correlations: No correlations between the passive binding, and active binding task and the LI were observed in the patient group (all $p>0.05$ after correction). A significant positive correlation was found between the BaBp contrast ($r=0.63$, $p=0.016$, corrected) and the SLF II LI in patients. On the other hand, no significant correlations were observed between all tasks and the SLF II LI in controls ($r=0.02$, $p=0.96$). Finally, no correlations were observed between all tasks and LI of the arcuate fasciculus for both groups (all $p>0.05$, after correction) (See Table VIII and IX)

Table VIII: *Pearson Correlations Between the Tasks and the LI Values of the SLF II and Arcuate Fibres, Control Group*

	Controls		Patient	
	Passive Binding	**Active Binding**	**Passive Binding**	**Active Binding**
LI SLF II	r=0.03, p=0.99	r=0.07, p=0.81	r=0.28, p=0.34	r=0.59, p=0.03
LI Arcuate	r=0.23, p=0.40	r=0.21, p=0.44	r=-0.04, p=0.89	r=-0.04, p=0.90

Table IX: *Pearson Correlations Between the Tasks and the LI Values of the SLF II and Arcuate Fibres, BaBp Contrast*

	Controls	Patients
	BaBp Contrast	**BaBp Contrast**
LI SLF II	r=0.02, p=0.96	**r=0.63, p=0.02***
LI Arcuate	r=0.10, p=0.71	r=-0.02, p=0.93

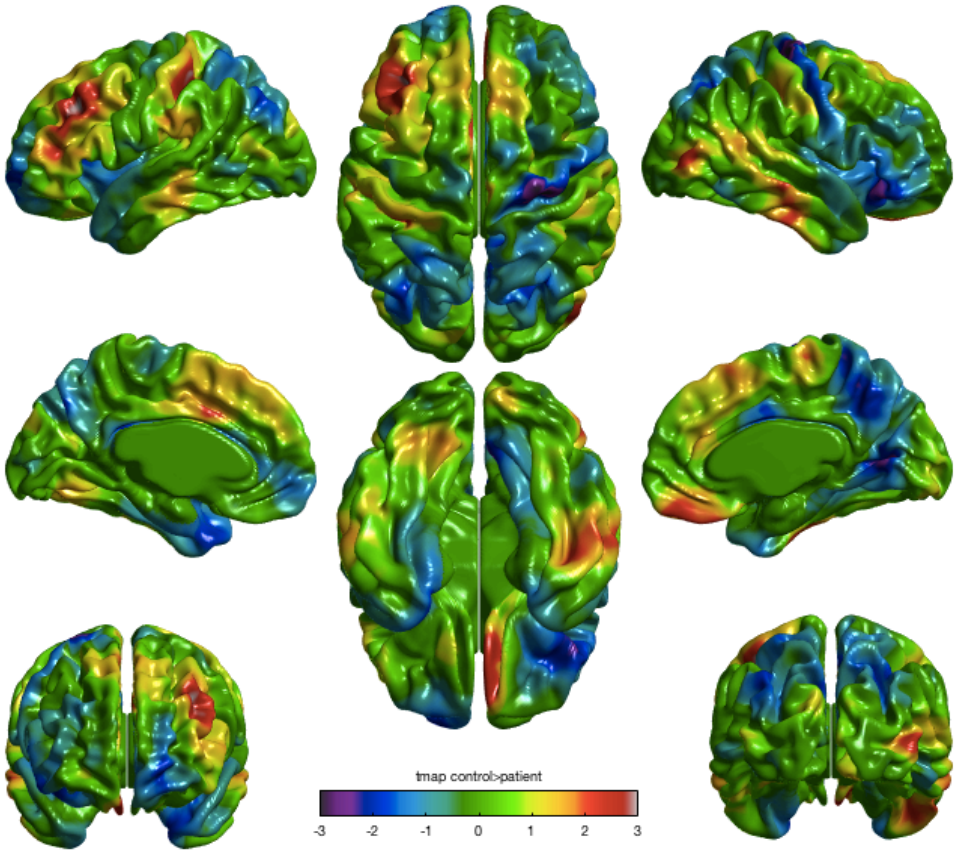
* Significant correlations corrected FDR

3. Cortical Thickness

Group differences

A whole brain analysis was performed. Figure 14 shows a t-value map in the Controls>Patients contrast. A positive t-value refers to an area in which controls have a greater cortical thickness than patients. However, no significant group difference in cortical thickness was observed ($p>0.05$, RFT). This goes in line with the absence of group differences in all the fibres analyzed during our DWI study.

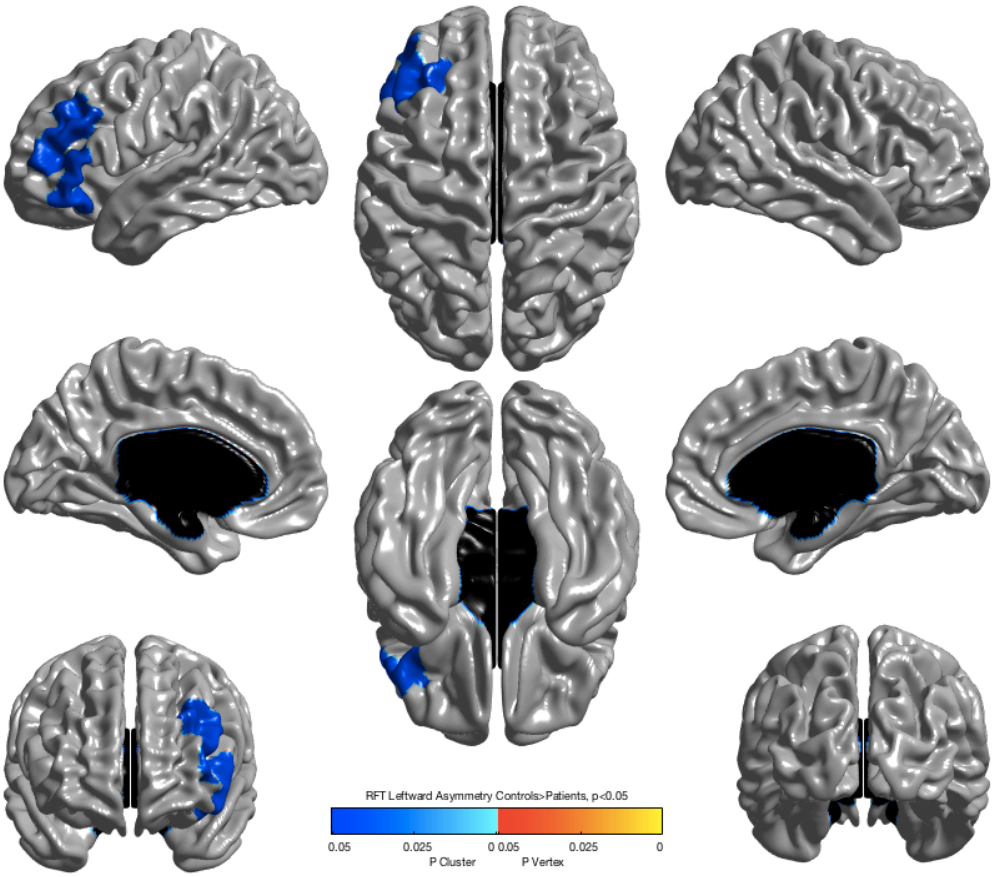
Figure 14: *Control>Patient T-map of Cortical Thickness*



Exploratory Analysis: Asymmetry

As for the exploratory analysis, a cortical thickness asymmetry study was performed with an alpha value of 0.05, RTF. A significant cluster was identified in the Control>Patient contrast, measuring 1601 vertex, with p=0.04 (Figure 15). This region was located in the prefrontal cortex, and presented a greater leftward asymmetry in controls compared to patients. No significant cluster presented a greater right than left asymmetry for this contrast. Naturally, the identical cluster was significant for the Patient>Control contrast, in which patients had a greater right than left asymmetry of that region.

Figure 15: *Cluster Representing the Area in which Controls have a Greater Leftward Cortical Thickness Asymmetry than Patients*.



The peak with the highest t-value (t=3.44) was extracted from this significant cluster, with MNI coordinates of (-45.9, 34.7, 30.2). According to the AAL atlas, this corresponds to the left middle frontal gyrus (MGF). Values were extracted by using a circular 10 mm radius mask.

Group comparison: ROI group difference was confirmed using One-Way ANOVA (F (1,27)=10.38, p=0.003, η^2=0.28).

Pearson Correlations: A significant positive correlation between the BaBp value and the MFG asymmetry values (r=0.64, p=0.01, corrected) was observed in controls, while it was non-significant in the patients group (r=0.49, p=0.08) All other correlations were non significant (all p>0.05, after correction) (See Table X and XI).

Table X: *Pearson Correlations Between Asymmetry Values of the MFG ROI and Task for both Groups.*

	Passive Binding	**Active Binding**
Controls	r=0.22, p=0.43	r=0.56,p=0.03
Patients	r=0.42 p=0.14	r=0.54, p=0.04

Table XI: *Pearson Correlations Between Asymmetry Values of the MFG ROI and BaBp Contrast for both Groups.*

	BaBp
Controls	**r=0.64, p=0.01***
Patients	r=0.49, p=0.08

* Significant correlations corrected FDR

Finally, as the SLF connects the middle frontal gyrus, correlations between the asymmetry index of the SLF and SLF II and the ROI were computed, to determine if the white matter correlated with the cortical thickness. No significant correlations were observed (Supplementary Table III).

Discussion

1. Summary of Results

The goal of this study was to investigate whether anatomical modifications could be responsible for the specific active binding impairment previously observed in schizophrenia (Grot, Petel Légaré et al. 2017). Using a subgroup of that article's participants, our results showed that, at a performance level, active binding was still specifically impaired in schizophrenic patients, while passive binding was spared (Grot, Petel Légaré et al. 2017). As for anatomical correlates, our main hypotheses were not confirmed by this study. Indeed, no alterations of the bilateral UF, the bilateral SLF, or any of its subcomponent were observed in patients with schizophrenia compared to healthy controls. Moreover, no significant correlations were observed between any of the fibre track studied and the task performance for both groups.

On the other hand, our exploratory studies revealed interesting results. Although there were no integrity alterations of both the UF LI and SLF LI in schizophrenic patients compared to controls, there was a relationship between the degree lateralization and task performance. Indeed, patients with a greater SLF leftward lateralization performed better in the executive aspect of the active binding task. Furthermore, in order to distinguish between parietal and temporal projections influences, the SLF II, connecting the DLPFC and the parietal cortex, as well as the arcuate fasciculus, connecting the prefrontal to the temporal cortex, were isolated. Once again, no alterations of the arcuate fasciculus or SLF II LI were observed in patients compared to controls, yet, patients presenting greater leftward lateralization of the SLF II performed better in the executive aspect of the active binding task. On other hand, our results showed that lateralization of the arcuate fasciculus did not have an influence the executive aspect of the active task, suggesting that the leftward prefrontal-parietal lateralization is specifically related the executive aspect of the active task in the patient group. Finally, no correlation between any lateralization values and task performances were observed in the control group.

As for our cortical thickness study, no group differences were observed, yet exploratory analyses yielded interesting results. The control group had a greater left than right MFG cortical thickness than the patient group. Moreover, a greater left than right cortical thickness in this region was related to a better performance in the executive aspect of the task in the control group, but not in the patient group. Our results will be discussed below.

2. Specific Active Binding Deficit in Schizophrenia

Our results replicated previous findings suggesting that patients have a specific active binding deficit, while passive binding is spared (Luck, Danion et al. 2010, Grot, Potvin et al. 2014). Indeed, patients performed significantly worse in the active task compared to the control group. On the other hand, both groups performed equally in the passive binding condition. This result is not surprising as our population is a subgroup of our previous study (14 of the 19 patients, and 15 of the 23 controls used in the previous study). However, it was essential to verify the survival of this group difference, owing that a number of participants were excluded. The specific active binding deficit observed goes in line with the meta-analysis results, as well as other studies stipulating that passive binding processes are spared in schizophrenia (Luck, Danion et al. 2010, Grot, Potvin et al. 2014). On the other hand, the specific active binding deficit could be due to a number of dysfunctional processes, which will be explored below.

a) Active Binding and Passive Binding in Schizophrenia

A number of processes are required to a greater extent during the active binding task compared to the passive binding task. Indeed, active binding requires attentional and manipulative processes, as well as encoding strategies, which would be less necessary during passive binding (Karlsen, Allen et al. 2010, Grot, Petel Légaré et al. 2017). First, encoding strategies would be necessary to a greater extent during the active task than the passive task, as an appropriate link needed to be created between the word (e.g. red word), and the colour-matched the spatial location (e.g. red ellipse), requiring the "colour-matching rule" to dominate. Second, attentional processes would be more

necessary in the active task than the passive task. As the words and spatial locations were separated in the active binding task, it would require more attentional switching and control in order to attend all stimuli (Corbetta, Shulman et al. 1995). Moreover, rule implementation, such as "colour-matching rule", is also moderated by attentional processes (Luck and Gold 2008). Third, manipulation would be required in the active task, as individuals needed to properly reorganize and associate the appropriate word and spatial location in that condition. Conversely, manipulation would not be as crucial in the passive task as the words and spatial locations were already associated. Interestingly, all those functions have been documented as impaired in schizophrenia (Fioravanti, Carlone et al. 2005, Ehrlich, Brauns et al. 2012, Fioravanti, Bianchi et al. 2012, Park and Gooding 2014). Therefore, a deficit in all or any of those three functions could underlie our performance results.

According to the working memory model proposed by Baddeley and colleagues (2011), the integration of association visuospatial and verbal stimuli information would occur in the episodic buffer. Thus, as patients do not present a deficit in the passive binding condition, this result implies that the episodic buffer function would be spared in schizophrenia. Moreover, according to Baddeley's model, the episodic buffer has a passive function, but could also have an active function when controlled by the central executive (Baddeley, Allen et al. 2011). Indeed, the passive function of the episodic buffer, integrating visuospatial and phonological information, could occur because of its link between the two slave systems, and would require the central executive's control to a lesser extent. On the other hand, during the active binding task, the two slave systems, the episodic buffer, as well as the control of the central executive would be required. Interestingly, manipulative, attentional functions as well as encoding strategies are held in the central executive (Baddeley, Allen et al. 2011). Following this logic, if the central executive were deficient in schizophrenia, it could underlie the specific active binding deficit in schizophrenia observed in this study. Accordingly, numerous studies propose that the central executive is specifically impaired in schizophrenia (Leiderman and Strejilevich 2004, Barch 2005, Oram, Geffen et al. 2005, Barch and Ceaser 2012). Our results support this, as only active binding performance, requiring the control of the central executive to a greater extent, is affected in patients with schizophrenia.

Nevertheless, it is important to mention that we cannot exclude the involvement of the central executive entirely during the passive binding task, as attentional processes, which are distributed by the central executive, are necessary to maintain information into memory (Gazzaley and Nobre 2012). The distinction between attentional processes during the passive and the active binding condition could be explained by a number of hypotheses. First, the new model by Baddeley (2012) posits that maintenance of simple information could be passive, which goes in line with our results. Indeed, Baddeley (2012) argues that tasks such as repeating numbers would not disrupt central executive functions, which he argued is due to the task's low attentional demands. In this view, maintenance of already bound information (passive binding) would not require the central executive, while complex information requiring manipulation, such as the active binding condition, would impose higher attentional demands. Second, applying this result to Cowan's model, patients could be deficient in the control of attention, but not in the focus of attention. Indeed, the maintenance of bound information could be spared in passive binding, as patients would be able to focus their attention on their internal representation. On the other hand, appropriate encoding and maintenance would be impaired in active binding, as it would require more attentional control to properly attend and associate the words and spatial locations. Third, the specific active binding deficit could also be due to impaired control of attention, but spared implementation of attention, as hypothesized by Luck and Gold (2008). The spared implementation of attention, which is the ability to increase processing of one stimulus while decreasing another, would allow patients to maintain the association's representation in memory during the passive task. Conversely, impaired control of attention would lead to inappropriate encoding and manipulation during active binding. Taken together, all those hypotheses imply that attentional processes such as focusing on simple stimuli would be spared in schizophrenia, while the control of attention, which requires more executive processes, would be impaired. This could thus contribute to a specific active binding deficit.

b) Encoding and Maintenance in Schizophrenia

As mentioned, both encoding and maintenance deficits have been documented to contribute to working memory deficits in schizophrenia (Spindler, Sullivan et al. 1997,

Kim, Glahn et al. 2004, Lee and Park 2005, Keedy, Ebens et al. 2006, Hahn, Robinson et al. 2010, Mayer and Park 2012, Park and Gooding 2014). The specific active binding deficit also suggests that both might contribute to the observed impairment.

First, maintenance deficits in schizophrenia were hypothesized to be mostly due to reduced attentional control, which increases distractibility, and disturbs the focus on internal representations (Hahn, Robinson et al. 2010). Patients were able to maintain the representation of the association between spatial location and the verbal information in memory, as illustrated by the intact passive binding performance. On the other hand, patients had a lower performance in the active binding task compared to controls. This observed specific active binding deficit would not be due to reduced visuospatial or verbal memory in schizophrenia, as the same amount of information needed to be remembered in both conditions (i.e. three words and three spatial locations) (Grot, Petel Légaré et al. 2017). As both condition required maintenance of bound information (i.e word and spatial location), it would be tempting to suggest that the active binding deficit is not due to impaired function during the maintenance phase. Yet, we cannot exclude the possibility that maintenance is affected, as the cognitive processes behind maintenance of actively and passively bound information could be different (Morey 2011). Indeed, maintenance requires the ability to focus attentional processes towards internal representations, and some studies propose that maintenance of actively bound information could demand more attentional processes (Morey 2011). Moreover, manipulation of information could occur during the delay, and contribute to the specific active deficit, as patients would fail to properly reorganize the information (i.e. associating the right word with the appropriate spatial location) (Crone, Wendelken et al. 2006, Park and Gooding 2014).

Second, encoding impairments could also contribute to the specific active binding deficit. Indeed, the main difference between active binding and passive binding is that perceptually, the information is already bound in the latter condition. This difference is thus present during encoding, as active binding requires individuals to make the association mentally and voluntarily. Therefore, the specific active binding deficit observed in patients could imply that the appropriate creation and encoding of the association between a word and a spatial location is impaired (Grot, Petel Légaré et al.

2017). This initial step could thus underlie the active binding deficit observed in this study. This is supported by numerous studies suggesting that working memory impairment in schizophrenia is due to inappropriate encoding (Lee and Park 2005, Hahn, Robinson et al. 2010, Mayer and Park 2012, Park and Gooding 2014). Nevertheless, it is important to mention that as our study focuses on anatomical correlates, it is not possible to verify activation failure during the various phases of the binding task. However, we propose that the deficit could occur during encoding, and that a possible maintenance deficit could also contribute to the impairment, a hypothesis supported by our previous study (Grot, Petel Légaré et al. 2017). Indeed, alterations in activation in the patient group were observed during both encoding and early maintenance (Grot, Petel Légaré et al. 2017).

In summary, the specific active binding deficit observed in this study is important, as it disentangled important aspects of working memory impairments in schizophrenia. First, our results support the hypothesis that patients have a deficit in higher cognitive processes such as attentional processes, encoding strategies, and manipulation. This has been documented before (Barch and Ceaser 2012) in tasks such as updating (Galletly, MacFarlane et al. 2007), manipulation (Kim, Glahn et al. 2004), inhibition of distractors (Hahn, Robinson et al. 2010, Smith, Eich et al. 2011), and planning (Morris, Rushe et al. 1995). Second, this specific deficit supports the highly replicated finding of impaired encoding in schizophrenia, but could also support possible impaired maintenance in schizophrenia, especially as manipulation could occur during this phase. This is in part corroborated by our previous study, as altered activation was observed during encoding and early maintenance in the patient group (Grot, Petel Légaré et al. 2017). Third, the specific active binding deficit also suggests that the main dysfunction could be created by the failure of the central executive's control, and not the episodic buffer. This might explain why there was no effect of the prefrontal-temporal network on performance, as the central executive, represented by the prefrontal-parietal network, would be mostly responsible for this deficit. Indeed, it is hypothesized that the prefrontal-parietal network is related to a number of processes held by the central executive (Wager and Smith 2003, Rottschy, Langner et al. 2012). Accordingly, our exploratory studies yielded interesting results supporting both Baddeley's working memory model, as well as an alteration in the

prefrontal-parietal network causing an active binding deficit in schizophrenia. This will be described in the next section.

3. Prefrontal-Parietal Network Leftward Lateralization Contributes to the Executive Aspect of the Active Binding Task

a) Prefrontal-Parietal Network

The SLF, and more specifically the SLF II is an important link between the prefrontal and parietal cortices (Petrides and Pandya 2002, Catani and de Schotten 2012, Wassermann, Makris et al. 2016). We observed that the leftward lateralization values of both fibres were related to the executive aspect of the task in patients. The executive aspect of the active binding task value was obtained by comparing the two binding conditions, and is thought to represent, in part, attentional processes, manipulation, and encoding strategies, which are required specifically during the active binding task. Our results are interesting as lateralization values are related only to the executive aspect of the active binding task, and not to the passive binding task in the patient group. Moreover, our results show that this relationship involves the prefrontal-parietal network specifically, as illustrated by the absence of correlation between performance on this aspect of the task and the arcuate fasciculus LI. Interestingly, the prefrontal-parietal network, represented in our study by the SLF and SLF II, is responsible for a number of functions held by the central executive, and which we hypothesized to contribute to the active binding deficit in the patient group (Wager and Smith 2003, Rottschy, Langner et al. 2012).

The possible altered involvement of this network in the specific active binding deficit observed in schizophrenia was also reported by our previous study (Grot, Petel Légaré et al. 2017). Indeed, we observed that the posterior parietal cortex and the left frontal cortex were hypoactivated in patients compared to controls during encoding. Moreover, altered left prefrontal cortex activation during early maintenance was reported in patients. This is interesting as those results are in line with our current study, which is composed of a subgroup of this study. Indeed, both studies suggest that an alteration of the left prefrontal-parietal network could explain the specific active binding in schizophrenia, as

illustrated by the relationship between anatomical values of this network (here, leftward lateralization of the SLF, and SLF II), and the executive aspect of the task in patients. Following this, it would be tempting to suggest that anatomical modifications would lead to a disconnection, and create the altered activations observed in our published study. Indeed, a recent study showed that there was a correlation between the functional activation of parietal and prefrontal regions, and the FA connecting those two regions (Olesen, Nagy et al. 2003). Yet, in order to confirm that this applies to our population, it would be important to first verify that the same altered activations are found in our subgroup, and second, that the anatomical modifications are related to the altered activations.

Nevertheless, unlike our previous study, which reported that an alteration of the left prefrontal-parietal network was involved specifically in the active binding deficit in schizophrenia, our results show that the leftward lateralization of this circuit is crucial for the executive aspect of the task. Therefore the possible functional impact of the lateralization of this network will be explored below.

b) White Matter: Leftward Lateralization of the Prefrontal-Parietal Network

Our results show that lateralization is especially important during the executive aspect of the task. Yet, it is important to mention that a high tendency between the active binding task and the leftward lateralization values were also observed in the patient group, but it did not survive the multiple comparison corrections. The stronger relationship between the executive aspect of the active task, and the lateralization might be due to its more focused representation of manipulation, encoding strategies as well as attentional processes, which are specifically disturbed in schizophrenia (Fioravanti, Carlone et al. 2005, Ehrlich, Brauns et al. 2012, Fioravanti, Bianchi et al. 2012, Park and Gooding 2014). Indeed, the prefrontal-parietal network is related to attentional processes (Awh, Anllo-vento et al. 2000, Müller and Knight 2006, Sharma, Weisbrod et al. 2011, Rottschy, Langner et al. 2012), encoding strategies (Owen, McMillan et al. 2005), as well as manipulative processes (Owen, Evans et al. 1996, Smith and Jonides 1999, Wagner,

Maril et al. 2001, Wager and Smith 2003, Crone, Wendelken et al. 2006, Park and Gooding 2014). As we previously hypothesized, a deficit in one or all of those functions could lead to the specific active deficit seen in patients. Therefore, it is possible that aberrant SLF and SLF II lateralization might underpin those dysfunctions of schizophrenia. Those hypotheses will be discussed below.

Encoding Strategies and Lateralization

Encoding processes have been documented as lateralized, which could underlie the advantage of the SLF and SLF II lateralization. It was observed that verbal and non-verbal material were encoded differently by the prefrontal cortex (Opitz, Mecklinger et al. 2000). In one study, participants had to either judge the loudness of a sound (non-verbal task), or the verbalization of a sound (verbal task) (Opitz, Mecklinger et al. 2000). This was followed by a recognition test. Encoding verbal material elicited left frontal hemisphere activity, while the right frontal hemisphere was recruited for non-verbal information. This PFC functional lateralization during encoding has been replicated numerous times (D'Esposito, Aguirre et al. 1998, Opitz, Mecklinger et al. 2000, Spence, Grasby et al. 2000, Walter, Wunderlich et al. 2003, Floel, Poeppel et al. 2004, Angrilli, Spironelli et al. 2009). Supporting the SLF preferential left hemispheric involvement during verbal tasks, one study showed that verbal working memory task performance correlated with the left, but not the right SLF FA in both the control and patient group (Karlsgodt, van Erp et al. 2008). Moreover, left SLF FA reduction, but not right SLF FA reduction in patients with schizophrenia was linked to their verbal working memory deficits (Karlsgodt, van Erp et al. 2008). Finally, in a verbal relational encoding study, establishing associative strategies activated the bilateral inferior frontal gyrus, with a more important left hemisphere involvement (Addis and McAndrews 2006). This is important, as it implies that encoding strategies for verbal information might be lateralized to the left.

In our study, an increased leftward lateralization of the SLF and SLF II was related to a better performance on the executive task in the patient group. The leftward advantage could be due to the verbal aspect of our task. Indeed, our task contained verbal information (words), which would preferentially be encoded by left hemisphere.

Moreover, the leftward lateralization could increase the ability to find effective verbal encoding strategies (Addis and McAndrews 2006). Therefore, the SLF and SLF II leftward lateralization could increase performance on the executive aspect of the active binding task, as it would allow proper encoding of the three presented words, as well as increase encoding strategies to create an appropriate link with their respective spatial positions using the "colour-matching rule". A reduction of this leftward lateralization could lead to a reduced capacity to use the appropriate encoding strategies between words and spatial locations. This would lead individuals to hold in an inadequate representation in memory, as illustrated by the lower performance of the patients having less SLF and SLF II leftward lateralization. Finally, as active binding requires more verbal encoding strategies, leftward lateralization of the prefrontal-parietal network would affect to a greater extent the active than the passive task performance, as seen with the absence of relationship between lateralization values and passive binding task in the patient group.

Manipulation, Attentional Processes and Lateralization

Brain lateralization is thought to be related in part to functional specialization (Toga and Thompson 2003). Indeed, the benefit of increased brain lateralization would be related to unilateral function, as it would increase efficiency, and reduce interference between various processes (Toga and Thompson 2003, Gotts, Jo et al. 2013, Chen and Omiya 2014). Accordingly, the advantage provided by an increased leftward asymmetry could be due to increased hemisphere specialization (Toga and Thompson 2003, Chen and Omiya 2014). Our task involved both visuospatial and verbal information. Moreover, the lateralization of the SLF has been linked to visuospatial and verbal processes (Catani, Allin et al. 2007, de Schotten, Dell'Acqua et al. 2011, Chechlacz, Gillebert et al. 2015). As the SLF seems to be involved in both visuospatial and verbal functions, and that our task required both modalities, the lateralization could therefore have a great impact on performance, especially during the active task. This hypothesis will be exposed below.

During the active task, three words and three spatial locations needed to be encoded separately into memory, and then appropriate associations would be made through manipulative processes, a function held by the prefrontal-parietal network, and represented in our study as the SLF and SLF II. An increased lateralization might be advantageous in the active task as hemispheric specialization could allow successful

separate encoding of verbal and spatial information, which could then be manipulated (Quak, London et al. 2015). Therefore, manipulative processes could be improved with increased lateralization, as it would allow the distinctive treatment of visuospatial and verbal information, thus making the creation of links between the three presented words and spatial locations more straightforward. This is illustrated in our results by greater performance on the executive aspect of the task with an increased SLF and SLF II lateralization in the patient group. On the other hand, the relationship between leftward asymmetry of the SLF and SLF II was not found for the passive task in the patient group. This could be due to the reduced need of separate verbal and visuospatial information encoding. Indeed, the main difference between the two tasks is that the information is already integrated in the passive condition (the word is already in its spatial location). Thus, this could lead to the spatial and verbal information to be perceived as a whole automatically, reducing the need for hemispheric specialization to promote manipulative processes (Quak, London et al. 2015). This was suggested in part by a study conducted by Prabhakaran, Narayanan et al. (2000). Their task also used verbal and spatial information that was presented either as bound (passive binding), or that was presented as separated and needed to be associated (active binding). An association of verbal and spatial information was then presented, and participants had to determine if they had seen it during the encoding phase. The authors observed that participants responded quicker and more accurately when information was already bound compared to when it was presented separately (Prabhakaran, Narayanan et al. 2000, Quak, London et al. 2015). This might suggest that perceptually, participants saw the combined information as an integrated whole in the passive condition, while in the active condition, they processed the information as two stimuli which then needed to be combined (Talsma 2015). Therefore, the increased hemispheric specialization created by lateralization could benefit the active task to a greater extent, as manipulative processes are only needed in that condition. This goes in line with our results as they suggest that the increased lateralization is beneficial for the executive aspect of the active binding task, but not the passive binding task in patients.

Lastly, the specialization of hemispheres could also benefit attentional processes. Attentional processes are related to manipulation, as one of the central elements of manipulation is the steady orientation of the attention to internal representation (Park and Gooding 2014). Visuospatial attention, and attentional processes are segregated to the right hemisphere (Gotts, Jo et al. 2013), and the right lateralization of the SLF II has been related to visuospatial attention (de Schotten, Dell'Acqua et al. 2011). Therefore, it is also possible that attentional processes are associated with careful circuit lateralization. Indeed, increased lateralization of attentional processes could influence the active binding task in the same way as manipulation, as attentional focus on internal representation would be required for adequate manipulation. Thus, schizophrenic patients might benefit of an increased leftward lateralization, as it would properly distribute attentional processes between hemispheres.

Finally, our anatomical results also go in line with the working memory model by Baddeley and colleagues (Baddeley, Allen et al. 2011). First, the visuospatial sketchpad and the phonological loop are separated subsystems, and lateralization could be important for their segregation, as lateralization could increase specialization. Then, integration into a coherent whole of visuospatial and phonological information would be performed in the episodic buffer, and the additional control of the central executive would be required during the active binding task. As hypothesized, the prefrontal-parietal network, represented by the SLF II, is related to a number of central executive's function. This goes in line with our results, as the SLF II leftward lateralization is related to the executive portion of the active binding task in patients, and that aspect of the task would be related to functions held by the central executive. Our result suggests that the SLF II leftward lateralization could improve the function of the central executive during the active task by promoting either manipulative, attentional, or encoding strategies process, or a combination of the three. Furthermore, the observed absence of lateralization effect in the passive task in patients also fits with Baddeley's working memory model. Indeed, in the passive binding task, information (here words and spatial locations) would be treated by the visuospatial sketchpad and the phonological loop respectively, and passively integrated together in the episodic buffer, without the central's executive control. As the two information would require less of the central executive's control,

there would be less benefit of treating the location and word separately. Taken together, our results suggest that the SLF and SLF II are related to the central's executive function, and that careful lateralization of this fibre increases its function, thereby benefiting the active binding task specifically.

Nevertheless, it is important to mention that further studies need to be conducted in order to determine if encoding strategies, manipulation, and/or attentional are influenced by SLF and SLF II lateralization. For example, it would be interesting to determine whether the lateralization benefit would be lost if the task involved binding of two stimuli from the same modality. Indeed, we argue that the benefit occurs, in part, due to visuospatial and verbal specialization during their encoding. Therefore, if both stimuli were, for example visuospatial, this advantage could be lost. However, for the purpose of this study it was essential to have both visuospatial and verbal information, in order to determine if the episodic buffer was altered in schizophrenia. Finally, our white matter results link the executive aspect of the active task to the lateralization of the prefrontal-parietal network. Interestingly, our gray matter results also support the importance of leftward lateralization of the prefrontal cortex during the executive aspect of the task. They will be exposed below.

c) Gray Matter: Prefrontal Lateralization

In our study, patients had a significantly smaller leftward MFG cortical thickness lateralization compared to controls. This MFG leftward lateralization has been documented in healthy adults (Luders, Narr et al. 2006, Plessen, Hugdahl et al. 2014). Moreover, reduction of left hemisphere dominance has been observed in patients with schizophrenia, and has been linked to the severity of symptoms (Oertel,Knöchel et al. 2010, Ribolsi 2009). Indeed, it was hypothesized that a number of symptoms of schizophrenia are related not only to the failure to establish left hemisphere dominance, but also to the increased involvement of the right hemisphere in language functions, leading to several symptoms (Mitchell and Crow 2005). Exemplifying this, a study by Walter, Wunderlich et al. (2003) showed that healthy controls had a left frontal cortex dominance during verbal working memory, and a right frontal cortex dominance for spatial working memory. On the other hand, this dominance was lost in schizophrenic

patients, and patients even showed a negative relationship between the activation of the right frontal area and verbal working memory (Walter, Wunderlich et al. 2003).

This goes in line with our cortical thickness results. Indeed, our results show that controls performed better in the executive aspect of our task when they had an increased leftward lateralization of the prefrontal cortex, but this advantage was not present in patients. Moreover, this relationship was only present for the executive aspect of the task in the control group. This implies that increased hemispheric specialization could improve attentional and manipulative processes, as well as encoding strategies, in the control group, while this advantage would be lost in patients. It is interesting to see that gray matter lateralization correlates with the executive aspect of the task in controls, but not in patients. Indeed, the fact that patients did not present this correlation could be explained by two non-mutually exclusive hypotheses. First, it is possible that patients do not have a relationship between the gray matter lateralization and the executive aspect of the task as they have a reduced leftward lateralization of this region, as illustrated by the group differences. Second, this could be due to the reduced leftward lateralization of the fibre connecting the prefrontal to the parietal cortex. Indeed, if the SLF, and SLF II lateralization were inadequate in patients, the advantage of the prefrontal cortical thickness leftward lateralization during the executive aspect of the task would be lost, as illustrated by the absence of correlation with gray matter lateralization in the patient group. In short, the lack of correlation between the executive aspect of the task, and the leftward prefrontal cortical thickness lateralization could be due to reduced leftward lateralization of the white matter connecting it to other regions. Therefore, an increased gray matter leftward lateralization would not be as beneficial, as its connectivity itself would be aberrant. This hypothesis also fits with our white matter results, which revealed that patients had a correlation between the leftward lateralization of the SLF and SLF II, while there was no effect in controls. This might come from the fact that SLF and SLF II lateralization is a limiting factor in patients, which could underpin the greater lateralization effect in that group.

Finally, it is important to assess why we observed cortical thickness lateralization group differences, but no SLF or SLF II LI group differences. Indeed, our white matter study showed a lateralization effect, but no group differences. This could be explained by

several factors. First, the literature on SLF lateralization is heterogeneous. Indeed, in healthy subjects, the SLF, and especially its temporal connection has been observed as left lateralized (Powell, Parker et al. 2006, Catani, Allin et al. 2007, Vernooij, Smits et al. 2007), while the SLF II has been observed as symmetrically distributed (Powell, Parker et al. 2006, de Schotten, Dell'Acqua et al. 2011), or lateralized to the right (Chechlacz, Gillebert et al. 2015). Lateralization thus seems to be a carefully regulated balance, rather than absolute hemispheric asymmetry. Second, the decreased leftward lateralization cortical thickness in patients encompasses a large prefrontal area. Therefore, a reduction of the prefrontal white matter leftward asymmetry might not be fully represented by the SLF or the SLF II. Indeed, those fibres are only part of the circuit connecting the prefrontal cortex to other regions, which could explain the lack of absolute lateralization. All in all, even if no group differences were found for the SLF and SLF II, our gray and white matter studies revealed a clear link and alteration between the executive aspect of the active binding task and the left lateralization of the prefrontal-parietal network. This suggests that there could be a possible attenuation in this network's lateralization in patients with schizophrenia.

Lastly, our results are interesting as the prefrontal-parietal network reorganization occurs until early adulthood, and corresponds to the onset of the disease (Canu, Agosta et al. 2015). The SLF is one of the last connections to be myelinated (Clemm von Hohenberg, Pasternak et al. 2014, Lett, Voineskos et al. 2014). Indeed, a study showed that the majority of white matter development occurs after birth, and that the SLF reaches 90 % of its development between the ages of 13 to 20 (Lebel, Walker et al. 2008). Instauration of the SLF lateralization also occurs during development, and was hypothesized to represent network maturity, and specialization in order to increase efficiency (Lebel, Walker et al. 2008, Catani and de Schotten 2012, Zhou, Lebel et al. 2013). This also applies to gray matter, as studies show that the VLPFC matures before the DLFPC (Gogtay, Giedd et al. 2004), and that the development of the latter is related to higher cognitive processes (Crone, Wendelken et al. 2006). In that study, the gray matter development, and more particularly of the DLPFC, was related to increased manipulation capacities (Crone, Wendelken et al. 2006). Supporting this, the development of the left prefrontal-parietal network was related to the development of

working memory capacity (Karlsgodt, Sun et al. 2008, Vestergaard, Madsen et al. 2011). The effect of age on our white matter and gray matter lateralization results was thus conducted in order to establish if this applied to our studied group. No correlations between age and neither left nor right FA, or with cortical thickness values for both groups were found. Surprisingly, there was a significant negative correlation between age and the SLF asymmetry in controls, but not in patients (Supplementary Table VII). This decreased leftward lateralization in the control group could be explained by their age. Indeed, controls have a mean age of 33 years, and it is thought that SLF FA peaks around the mid-twenties, after which it decreases, a phenomenon hypothesized to be related to cognitive decline with age (Lebel, Gee et al. 2012, Olson, Heide et al. 2015). Hence, in order to study the effect of maturation of the SLF, participants from childhood to teenage years would have been more appropriate. Nevertheless, our study could still suggest that improper lateralization during neurodevelopment could cause schizophrenia symptoms, such as working memory deficit.

All in all, the prefrontal-parietal improper lateralization could cause a number of deficits in schizophrenia, which goes in line with cognitive findings. Indeed, the development of the network follows the progression of working memory deficits. As mentioned, cognitive deficits are observed during the premorbid phase, and can deteriorate at onset until they stabilize (Tandon, Nasrallah et al. 2009, APA 2013, Keefe 2014). Our results could suggest that this improper lateralization could affect cognitive functions of higher order, such as those held by the central executive in Baddeley's model, which was represented in this study as the executive aspect of the active binding task.

Limits

There are several limits to this study. Contrary to our hypotheses, no cortical thickness group differences were observed, and the two main fibre tracks studied were not significantly different between groups. It would be tempting to propose that this could be due to small sample size (15 controls and 14 patients), yet, effect sizes show that this is probably not the case. However, other limits could explain this absence of group difference in anatomical values, which are usually observed in the schizophrenic population.

First, all patients were taking medications. The most documented finding concerning the impact of medication is an increased basal ganglia volume (Celso Arango, Alan Breier et al. 2003, Buckley 2005), but it was also observed that patients who respond the most to antipsychotics usually have a restoration of anatomical values, in white and gray matter (Celso Arango, Alan Breier et al. 2003). Likewise, patients that have fewer anatomical abnormalities also respond better to treatment (Celso Arango, Alan Breier et al. 2003). Conversely, another study showed that long-term antipsychotic treatment reduced gray and white matter volumes (Ho, Andreasen et al. 2011), which was later replicated by a review combining 279 articles (Moncrieff and Leo 2010). Finally, antipsychotics also have an effect on cognition, but as mentioned, their effects on cognitive symptoms are low (Keefe, Silva et al. 1999). Antipsychotic treatment could therefore be an important cofounding factor of this study, as it could influence both anatomy and the cognition. Enrolling first-episode patients would have been advantageous, as it would have reduced the confounding factors, and even more so, as our study suggests that network maturation might be defective in schizophrenia. The inclusion of first-episode patients would control for various factors including medication, and duration of disease, as the latter influences anatomical values, with usually more widespread modification in chronic patients (Ellison-Wright, Glahn et al. 2008). However, we did not have access to that population. Nevertheless, the recent study of our laboratory showed that there was no correlation between the medication dosage and the activation levels or the performance in the patient group (Grot, Petel Légaré et al. 2017). Likewise, in the current study, no correlations were observed between medication

dosages as well as disease duration, and all performance or anatomical values. Therefore, we can suggest that medication and disease duration had little effect on our results.

Another important issue is that IQ did not significantly differ between our patient, and control group ($p=0.65$). As mentioned, the schizophrenic population generally has a lower IQ. A deficit in active binding performance was observed. Yet, working memory deficits are present when controlling for IQ (Kremen, Seidman et al. 2001, Bowie and Harvey 2006). Therefore, our patient group might be composed of a number of high-functioning patients, which might not be representative of the schizophrenic population in general. This might underpin the lack of anatomical differences in our study. However, we consider the fact that patients and controls have a matched IQ as an advantage in our case, as working memory performances are often correlates with IQ (Mohn, Sundet et al. 2014). Moreover, it was documented that IQ correlates to a greater extent with higher executive function, such as our active binding task (Ackerman, Beier et al. 2005). This is illustrated in our results as we observed a significant positive correlation for both groups between IQ and active binding performance, but not the passive task (Supplementary Table VI). Therefore, as IQ matches both groups, it allows us to correct this artefact, and suggests that lower IQ in the patient group did not influence our cognitive finding. Indeed, as both groups are matched in IQ, we can safely say that active binding deficit is not due to a generally lower IQ.

Furthermore, the relationship between handedness and brain lateralization is not fully understood (Good, Johnsrude et al. 2001). Yet, handedness sometimes has an influence on anatomy (Knecht, Dräger et al. 2000). For example, there is an over-representation of left-handed or ambidextrous individuals in schizophrenia, which could be related to aberrant lateralization of circuits (Gur 1977, Green, Satz et al. 1989, Crow 2000). This goes in line with our current study, as only one left-handed individual was included, which was a patient. Moreover this individual had the highest patient performance, as well as the highest leftward lateralization of both SLF and SLF II, which might be due to the fact that he has an increased left-lateralized brain. As our exploratory study is based on brain lateralization, it would have been advantageous to only have right-handed subjects in order to reduce this confounding factor. Therefore, in order to verify that this participant did not cause the whole effect, partial correlations, controlling

for handedness, were computed between the LI values of both white and gray matter and the task performances. However, the significant relationship between task performance and LI values were still present (Supplementary Table IV, V). Moreover, cortical thickness group difference in lateralization was also computed while correcting for handedness, and the group difference survived (Supplementary Figure 1). Therefore, we decided not to correct for laterality index for all tasks, as the group were matched by handedness ($p=0.33$).

Finally, the various methodologies all include limiting factors. First, all DWI, and especially deterministic tractography has the possibility of crossing fibres (Descoteaux and Poupon 2012). Crossing fibres refers to locations in which there is more than one single orientation. Deterministic tractography assumes there is one direction at each voxel, using only the principal eigenvector. It is therefore more vulnerable to noise, crossing fibres, or areas of high curvature (Descoteaux and Poupon 2012). However, in order to have a significant impact on the lateralization result, crossing fibres would have to be lateralized (Vernooij, Smits et al. 2007). Finally, the statistical threshold used for cortical thickness (RTF, $p<0.05$) was also quite liberal. However, we believe that it was adequate given the low number of participants.

Conclusion

Our previous study suggested that the specific active binding deficit could be underpinned by an alteration of the left prefrontal-parietal network (Grot, Petel Légaré et al. 2017). This network is responsible for various higher order processes such as manipulation, encoding strategies, and attentional processes, and could thus be responsible for this deficit. In this current study, we observed that anatomical modifications of the prefrontal-parietal network were related to the specific active binding deficit in schizophrenia. More specifically, the leftward lateralization of this network was altered in patients, suggesting that proper development and network formation is compromised in patients. This lateralization process occurs during development, and correlates disease onset. Our results thus support the neurodevelopmental hypothesis of schizophrenia, and highlight the importance of connectivity studies in patients with schizophrenia. Moreover, our results go in line with the prefrontal dysconnectivity hypothesis, which stipulates that hypofrontality would lead to a number of cognitive symptoms. Further anatomical studies have to be conducted on the prefrontal-parietal network in schizophrenia to determine whether this network is altered in patients, and related to other higher cognitive processes.

References

Abigail G. Garrity , M. D. Godfrey D. Pearlson , P. D. Kristen McKiernan , P. D. Dan Lloyd , P. D. Kent A. Kiehl and P. D. Vince D. Calhoun (2007). "Aberrant "Default Mode" Functional Connectivity in Schizophrenia." American Journal of Psychiatry **164**(3): 450-457.

Achim, A. M. and M. Lepage (2005). "Neural correlates of memory for items and for associations: an event-related functional magnetic resonance imaging study." Journal of cognitive neuroscience **17**(4): 652-667.

Ackerman, P. L., M. E. Beier and M. O. Boyle (2005). Working memory and intelligence: The same or different constructs?, American Psychological Association.

Ad-Dab'bagh, Y., Einarson, D., Lyttelton, O., Muehlboeck, J.-S., Mok, K., Ivanov, O., Vincent, R.D., Lepage, C., Lerch, J., Fombonne, E., and Evans, A.C. (2006). "The CIVET Image-Processing Environment: A Fully Automated Comprehensive Pipeline for Anatomical Neuroimaging Research." In Proceedings of the 12th Annual Meeting of the Organization for Human Brain Mapping, M. Corbetta, ed. (Florence, Italy, NeuroImage).

Ad-Dab'bagh, Y., Singh, V., Robbins, S., Lerch, J., Lyttelton, O., Fombonne, E., and Evans, A.C. (2005). "Native space cortical thickness measurement and the absence of correlation to cerebral volume." In Proceedings of the 11th Annual Meeting of the Organization for Human Brain Mapping, K. Zilles, ed. (Toronto, NeuroImage).

Addis, D. R. and M. P. McAndrews (2006). "Prefrontal and hippocampal contributions to the generation and binding of semantic associations during successful encoding." NeuroImage **33**(4): 1194-1206.

Andersson, J. L. R., S. Skare and J. Ashburner (2003). "How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging." NeuroImage **20**(2): 870-888.

Andersson, J. L. R. and S. N. Sotiropoulos (2016). "An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging." NeuroImage **125**: 1063-1078.

Angrilli, A., C. Spironelli, T. Elbert, T. J. Crow, G. Marano and L. Stegagno (2009). "Schizophrenia as Failure of Left Hemispheric Dominance for the Phonological Component of Language." PLOS ONE **4**(2): e4507.

Anticevic, A., G. Repovs and D. M. Barch (2011). "Working Memory Encoding and Maintenance Deficits in Schizophrenia: Neural Evidence for Activation and Deactivation Abnormalities." Schizophrenia Bulletin.

Anticevic, A., G. Repovs and D. M. Barch (2013). "Working Memory Encoding and Maintenance Deficits in Schizophrenia: Neural Evidence for Activation and Deactivation Abnormalities." Schizophrenia Bulletin **39**(1): 168-178.

Anticevic, A., G. Repovs, J. H. Krystal and D. M. Barch (2012). "A broken filter: Prefrontal functional connectivity abnormalities in schizophrenia during working memory interference." Schizophrenia Research **141**(1): 8-14.

APA (2013). Schizophrenia Spectrum and Other Psychotic Disorders. Diagnostic and Statistical Manual of Mental Disorders.

Atkinson, R. C. and R. M. Shiffrin (1968). "Human memory: A proposed system and its control processes." Psychology of learning and motivation **2**: 89-195.

Awh, E., L. Anllo-vento and S. A. Hillyard (2000). "The Role of Spatial Selective Attention in Working Memory for Locations: Evidence from Event-Related Potentials." J. Cognitive Neuroscience **12**(5): 840-847.

Baddeley, A. (2000). "The episodic buffer: a new component of working memory?" Trends in Cognitive Sciences **4**(11): 417-423.

Baddeley, A. (2003). "Working memory: looking back and looking forward." Nat Rev Neurosci **4**(10): 829-839.

Baddeley, A. (2007). Working memory, thought, and action, OUP Oxford.

Baddeley, A. (2010). "Working memory." Current Biology **20**(4): R136-R140.

Baddeley, A. (2012). "Working memory: theories, models, and controversies." Annual review of psychology **63**: 1-29.

Baddeley, A., R. Allen and F. Vargha-Khadem (2010). "Is the hippocampus necessary for visual and verbal binding in working memory?" Neuropsychologia **48**(4): 1089-1095.

Baddeley, A., C. Papagno and G. Vallar (1988). "When long-term learning depends on short-term storage." Journal of Memory and Language **27**(5): 586-595.

Baddeley, A. D. (1966). "Short-term memory for word sequences as a function of acoustic, semantic and formal similarity." Quarterly Journal of Experimental Psychology **18**(4): 362-365.

Baddeley, A. D., R. J. Allen and G. J. Hitch (2011). "Binding in visual working memory: The role of the episodic buffer." Neuropsychologia **49**(6): 1393-1400.

Baddeley, A. D. and G. Hitch (1974). "Working memory." Psychology of learning and motivation **8**: 47-89.

Baddeley, A. D. and G. Hitch (2010). "Working Memory " Scholarpedia **5**.

Baddeley, A. D., N. Thomson and M. Buchanan (1975). "Word length and the structure of short-term memory." Journal of Verbal Learning and Verbal Behavior **14**(6): 575-589.

Barch, D. M. (2005). "The cognitive neuroscience of schizophrenia." Annu. Rev. Clin. Psychol. **1**: 321-353.

Barch, D. M., J. Bustillo, W. Gaebel, R. Gur, S. Heckers, D. Malaspina, M. J. Owen, S. Schultz, R. Tandon, M. Tsuang, J. Van Os and W. Carpenter (2013). "Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: Relevance to DSM-5." Schizophrenia Research **150**(1): 15-20.

Barch, D. M. and A. Ceaser (2012). "Cognition in Schizophrenia: Core Psychological and Neural Mechanisms." Trends in cognitive sciences **16**(1): 10.1016/j.tics.2011.1011.1015.

Bench, C. J., C. D. Frith, P. M. Grasby, K. J. Friston, E. Paulesu, R. S. J. Frackowiak and R. J. Dolan (1993). "Investigations of the functional anatomy of attention using the stroop test." Neuropsychologia **31**(9): 907-922.

Bennett, I. J. and B. Rypma (2013). "Advances in functional neuroanatomy: A review of combined DTI and fMRI studies in healthy younger and older adults." Neuroscience & Biobehavioral Reviews **37**(7): 1201-1210.

Bleuler, E. (1951). "Dementia praecox or the group of schizophrenias." Journal of the American Medical Association **145**(9): 685-685.

Bor, D., J. Duncan, R. J. Wiseman and A. M. Owen (2003). "Encoding Strategies Dissociate Prefrontal Activity from Working Memory Demand." Neuron **37**(2): 361-367.

Boucher, M., S. Whitesides and A. Evans "Depth potential function for folding pattern representation, registration and analysis." Medical Image Analysis **13**(2): 203-214.

Bowie, C. R. and P. D. Harvey (2006). "Cognitive deficits and functional outcome in schizophrenia." Neuropsychiatric Disease and Treatment **2**(4): 531-536.

Bozikas, V. P., C. Andreou, M. Giannakou, T. Tonia, D. Anezoulaki, A. Karavatos, K. Fokas and M. H. Kosmidis (2005). "Deficits in sustained attention in schizophrenia but not in bipolar disorder." Schizophrenia Research **78**(2–3): 225-233.

Braff, D. L. (1993). "Information Processing and Attention Dysfunctions in Schizophrenia." Schizophrenia Bulletin **19**(2): 233-259.

Braff, D. L. (2015). "The importance of endophenotypes in schizophrenia research." Schizophrenia Research **163**(1–3): 1-8.

Brebion, G., X. Amador, M. Smith and J. Gorman (1997). "Mechanisms underlying memory impairment in schizophrenia." Psychological medicine **27**(02): 383-393.

Brébion, G., A. S. David, H. Jones and L. S. Pilowsky (2004). "Semantic Organization and Verbal Memory Efficiency in Patients With Schizophrenia." Neuropsychology **18**(2): 378-383.

Buchanan, R. W., A. Francis, C. Arango, K. Miller, D. M. Lefkowitz, R. P. McMahon, P. E. Barta and G. D. Pearlson (2004). "Morphometric assessment of the heteromodal association cortex in schizophrenia." American Journal of Psychiatry **161**(2): 322-331.

Buckley, P. F. (2005). "Neuroimaging of schizophrenia: structural abnormalities and pathophysiological implications." Neuropsychiatric Disease and Treatment **1**(3): 193-204.

Bunge, S. A., E. Hazeltine, M. D. Scanlon, A. C. Rosen and J. D. E. Gabrieli (2002). "Dissociable Contributions of Prefrontal and Parietal Cortices to Response Selection." NeuroImage **17**(3): 1562-1571.

Burglen, F., P. Marczewski, K. J. Mitchell, M. Van der Linden, M. K. Johnson, J.-M. Danion and P. Salamé (2004). "Impaired performance in a working memory binding task in patients with schizophrenia." Psychiatry research **125**(3): 247-255.

Burns, J., D. Job, M. E. Bastin, H. Whalley , T. MacGillivray, E. C. Johnstone and S. M. Lawrie (2003). "Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study." The British Journal of Psychiatry **182**(5): 439-443.

Bustini, M., P. Stratta, E. Daneluzzo, R. Pollice, P. Prosperini and A. Rossi (1999). "Tower of Hanoi and WCST performance in schizophrenia: problem-solving capacity and clinical correlates." Journal of Psychiatric Research **33**(3): 285-290.

Cameron S. Carter, Mark Mintun, Thomas Nichols and Jonathan D. Cohen (1997). "Anterior Cingulate Gyrus Dysfunction and Selective Attention Deficits in Schizophrenia: [15O]H2O PET Study During Single-Trial Stroop Task Performance." American Journal of Psychiatry **154**(12): 1670-1675.

Campo, P., C. Poch, F. B. R. Parmentier, S. Moratti, J. V. Elsley, N. P. Castellanos, J. M. Ruiz-Vargas, F. del Pozo and F. Maestú (2010). "Oscillatory activity in prefrontal and posterior regions during implicit letter-location binding." NeuroImage **49**(3): 2807-2815.

Canadian Psychiatric Association (2005). "CLINICAL PRACTICE GUIDELINES: Treatment of schizophrenia." Canadian Journal of Psychiatry **50**(13).

Cannon, T. D., D. C. Glahn, J. Kim and et al. (2005). "Dorsolateral prefrontal cortex activity during maintenance and manipulation of information in working memory in patients with schizophrenia." Archives of General Psychiatry **62**(10): 1071-1080.

Canu, E., F. Agosta and M. Filippi (2015). "A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease." Schizophrenia Research **161**(1): 19-28.

Carletti, F., J. B. Woolley, S. Bhattacharyya, R. Perez-Iglesias, P. Fusar Poli, L. Valmaggia, M. R. Broome, E. Bramon, L. Johns, V. Giampietro, S. C. R. Williams, G. J. Barker and P. K. McGuire (2012). "Alterations in White Matter Evident Before the Onset of Psychosis." Schizophrenia Bulletin **38**(6): 1170-1179.

Carol A. Tamminga, A. D. S., Anthony D. Wagner (2010). "The Hippocampal Formation in Schizophrenia." Am J Psychiatry(167): 1178–1193.

Carol A. Tamminga, A. D. S., Anthony D. Wagner (2010). "The Hippocampal Formation in Schizophrenia." The American Journal of Psychiatry **167**(10): 1178-1193.

Carpenter Jr, W. T. (2004). "Clinical constructs and therapeutic discovery." Schizophrenia Research **72**(1): 69-73.

Carpenter, W. T., Koenig,James I, (2008). "The Evolution of Drug Development in Schizophrenia." Neuropsychopharmacology **33**(9): 2061-2079.

Carter, J. D., J. Bizzell, C. Kim, C. Bellion, K. L. H. Carpenter, G. Dichter and A. Belger (2010). "Attention Deficits In Schizophrenia – Preliminary Evidence Of Dissociable Transient And Sustained Deficits." Schizophrenia research **122**(1-3): 104-112.

Catani, M., M. P. G. Allin, M. Husain, L. Pugliese, M. M. Mesulam, R. M. Murray and D. K. Jones (2007). "Symmetries in human brain language pathways correlate with verbal recall." Proceedings of the National Academy of Sciences of the United States of America **104**(43): 17163-17168.

Catani, M. and M. T. de Schotten (2012). Atlas of human brain connections, Oxford University Press.

Celso Arango, Alan Breier, Robert McMahon, J. William T. Carpenter, , and Robert W. Buchanan (2003). "The Relationship of Clozapine and Haloperidol Treatment Response to Prefrontal, Hippocampal, and Caudate Brain Volumes." American Journal of Psychiatry **160**(8): 1421-1427.

Chakos, M. H., S. A. Schobel, H. Gu, G. Gerig, D. Bradford, C. Charles and J. A. Lieberman (2005). "Duration of illness and treatment effects on hippocampal volume in male patients with schizophrenia." The British Journal of Psychiatry **186**(1): 26-31.

Chambon, V., N. Franck, E. Koechlin, E. Fakra, G. Ciuperca, J.-M. Azorin and C. Farrer (2008). "The architecture of cognitive control in schizophrenia." Brain **131**(4): 962-970.

Chechlacz, M., C. R. Gillebert, S. A. Vangkilde, A. Petersen and G. W. Humphreys (2015). "Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention." The Journal of Neuroscience **35**(30): 10647-10658.

Chen, C. and Y. Omiya (2014). "Brain asymmetry in cortical thickness is correlated with cognitive function." Frontiers in Human Neuroscience **8**: 877.

Chhabra, S., J. Badcock and M. Maybery (2013). "Memory binding in clinical and non-clinical psychotic experiences: how does the continuum model fare?" Cognitive neuropsychiatry **18**(4): 304-325.

Christensen, B. K., T. A. Girard and R. M. Bagby (2007). "Wechsler Adult Intelligence Scale-short form for index and IQ scores in a psychiatric population." Psychological assessment **19**(2): 236.

Ciapparelli, A., R. Paggini, D. Marazziti, C. Carmassi, M. Bianchi, C. Taponecco, G. Consoli, V. Lombardi, G. Massimetti and L. Dell'Osso (2007). "Comorbidity with axis I anxiety disorders in remitted psychotic patients 1 year after hospitalization." CNS Spectrums **12**(12): 913-919.

Cirillo, M. A. and L. J. Seidman (2003). "Verbal Declarative Memory Dysfunction in Schizophrenia: From Clinical Assessment to Genetics and Brain Mechanisms." Neuropsychology Review **13**(2): 43-77.

Clemm von Hohenberg, C., O. Pasternak, M. Kubicki, T. Ballinger, M.-A. Vu, T. Swisher, K. Green, M. Giwerc, B. Dahlben, J. M. Goldstein, T.-U. W. Woo, T. L. Petryshen, R. I. Mesholam-Gately, K. A. Woodberry, H. W. Thermenos, C. Mulert, R. W. McCarley, L. J. Seidman and M. E. Shenton (2014). "White Matter Microstructure in Individuals at Clinical High Risk of Psychosis: A Whole-Brain Diffusion Tensor Imaging Study." Schizophrenia Bulletin **40**(4): 895-903.

Collin, G., R. S. Kahn, M. A. de Reus, W. Cahn and M. P. van den Heuvel (2014). "Impaired rich club connectivity in unaffected siblings of schizophrenia patients." Schizophrenia bulletin **40**(2): 438-448.

Collins, D. L., Neelin, P., Peters, T.M., and Evans, A.C. (1994). "Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space." Journal of Computer Assisted Tomography **18**: 192-205.

Corbetta, M., G. L. Shulman, F. M. Miezin and S. E. Petersen (1995). "Superior parietal cortex activation during spatial attention shifts and visual feature conjunction." Science **270**(5237): 802.

Cornblatt, B. A. K., John G. (1994). "Impaired Attention, Genetics, and the Pathophysiology of Schizophrenia." Schizophrenia Bulletin **20**(1): 31-46.

Cowan, N. (1988). "Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system." Psychological bulletin **104**(2): 163.

Cowan, N. (2001). "The magical number 4 in short-term memory: A reconsideration of mental storage capacity." The Behavioural and Brain Sciences **24**(1): 87-114.

Cowan, N. (2008). "What are the differences between long-term, short-term, and working memory?" Progress in brain research **169**: 323-338.

Cowan, N., E. M. Elliott, J. S. Saults, C. C. Morey, S. Mattox, A. Hismjatullina and A. R. Conway (2005). "On the capacity of attention: Its estimation and its role in working memory and cognitive aptitudes." Cognitive psychology **51**(1): 42-100.

Craik, F. I. and R. S. Lockhart (1972). "Levels of processing: A framework for memory research." Journal of verbal learning and verbal behavior **11**(6): 671-684.

Crone, E. A., C. Wendelken, S. Donohue, L. van Leijenhorst and S. A. Bunge (2006). "Neurocognitive development of the ability to manipulate information in working memory." Proceedings of the National Academy of Sciences **103**(24): 9315-9320.

Crow, T. J. (2000). "Schizophrenia as the price that Homo sapiens pays for language: a resolution of the central paradox in the origin of the species." Brain Research Reviews **31**(2–3): 118-129.

D'Esposito, M., G. K. Aguirre, E. Zarahn, D. Ballard, R. K. Shin and J. Lease (1998). "Functional MRI studies of spatial and nonspatial working memory." Cognitive Brain Research **7**(1): 1-13.

D'Esposito, M., B. R. Postle and B. Rypma (2000). "Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies." Experimental Brain Research **133**(1): 3-11.

Daniel H. Mathalon, Theda Heinks and Judith M. Ford (2004). "Selective Attention in Schizophrenia: Sparing and Loss of Executive Control." American Journal of Psychiatry **161**(5): 872-881.

Davachi, L., J. P. Mitchell and A. D. Wagner (2003). "Multiple routes to memory: distinct medial temporal lobe processes build item and source memories." Proceedings of the National Academy of Sciences **100**(4): 2157-2162.

de Schotten, M. T., F. Dell'Acqua, S. J. Forkel, A. Simmons, F. Vergani, D. G. M. Murphy and M. Catani (2011). "A lateralized brain network for visuospatial attention." Nat Neurosci **14**(10): 1245-1246.

Dejerine, J. J. and A. Dejerine-Klumpke (1895). Anatomie des centres nerveux, Rueff.

Descoteaux, M. and C. Poupon (2012). "Diffusion-weighted MRI." Comprehensive Biomedical Physics **3**(6): 81-97.

Dickerson, B. C., E. Fenstermacher, D. H. Salat, D. A. Wolk, R. P. Maguire, R. Desikan, J. Pacheco, B. T. Quinn, A. Van der Kouwe, D. N. Greve, D. Blacker, M. S. Albert, R. J. Killiany and B. Fischl (2008). "Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths." NeuroImage **39**(1): 10-18.

Driesen, N. R., H.-C. Leung, V. D. Calhoun, R. T. Constable, R. Gueorguieva, R. Hoffman, P. Skudlarski, P. S. Goldman-Rakic and J. H. Krystal (2008). "Impairment of working memory maintenance and response in schizophrenia: functional magnetic resonance imaging evidence." Biological psychiatry **64**(12): 1026-1034.

Ehrlich, S., S. Brauns, A. Yendiki, B.-C. Ho, V. Calhoun, S. C. Schulz, R. L. Gollub and S. R. Sponheim (2012). "Associations of Cortical Thickness and Cognition in Patients With Schizophrenia and Healthy Controls." Schizophrenia Bulletin **38**(5): 1050-1062.

Elizabeth D. Radomsky, Gretchen L. Haas, J. John Mann and John A. Sweeney (1999). "Suicidal Behavior in Patients With Schizophrenia and Other Psychotic Disorders." American Journal of Psychiatry **156**(10): 1590-1595.

Ellison-Wright, I. and E. Bullmore (2009). "Meta-analysis of diffusion tensor imaging studies in schizophrenia." Schizophrenia Research **108**(1–3): 3-10.

Ellison-Wright, I., D. C. Glahn, A. R. Laird, S. M. Thelen and E. Bullmore (2008). "The Anatomy of First-Episode and Chronic Schizophrenia: An Anatomical Likelihood Estimation Meta-Analysis." The American journal of psychiatry **165**(8): 1015-1023.

Fang, X., Y. Wang, L. Cheng, Y. Zhang, Y. Zhou, S. Wu, H. Huang, J. Zou, C. Chen, J. Chen, H. Wang and T. Jiang (2017). "Prefrontal dysconnectivity links to working memory deficit in first-episode schizophrenia." Brain Imaging and Behavior: 1-10.

Fernández-Miranda, J. C., Y. Wang, S. Pathak, L. Stefaneau, T. Verstynen and F.-C. Yeh (2015). "Asymmetry, connectivity, and segmentation of the arcuate fascicle in the human brain." Brain Structure and Function **220**(3): 1665-1680.

Ferrand, L., B. New, M. Brysbaert, E. Keuleers, P. Bonin, A. Méot, M. Augustinova and C. Pallier (2010). "The French Lexicon Project: Lexical decision data for 38,840 French words and 38,840 pseudowords." Behavior Research Methods **42**(2): 488-496.

Fillard, P., X. Pennec, V. Arsigny and N. Ayache (2007). "Clinical DT-MRI estimation, smoothing, and fiber tracking with log-Euclidean metrics." IEEE transactions on medical imaging **26**(11): 1472-1482.

Finke, C., M. Braun, F. Ostendorf, T.-N. Lehmann, K.-T. Hoffmann, U. Kopp and C. J. Ploner (2008). "The human hippocampal formation mediates short-term memory of colour–location associations." Neuropsychologia **46**(2): 614-623.

Fioravanti, M., V. Bianchi and M. E. Cinti (2012). "Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence." BMC Psychiatry **12**(1): 64.

Fioravanti, M., O. Carlone, B. Vitale, M. E. Cinti and L. Clare (2005). "A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia." Neuropsychol Rev **15**.

Floel, A., D. Poeppel, E. A. Buffalo, A. Braun, C. W. H. Wu, H.-J. Seo, K. Stefan, S. Knecht and L. G. Cohen (2004). "Prefrontal Cortex Asymmetry for Memory Encoding of Words and Abstract Shapes." Cerebral Cortex **14**(4): 404-409.

Flyckt, L. M., Maria , Edman, Gunnar Carlsson,Roger and Cullberg, Jonhan (2006). "Predicting 5-Year Outcome in First-Episode Psychosis: Construction of a Prognostic Rating Scale. ." The Journal of Clinical Psychiatry **67**(7): 916-924.

Folsom, D. and D. V. Jeste (2002). "Schizophrenia in homeless persons: a systematic review of the literature." Acta Psychiatrica Scandinavica **105**(6): 404-413.

Fonov, V. S., A. C. Evans, R. C. McKinstry, C. R. Almli and D. L. Collins (2009). "Unbiased nonlinear average age-appropriate brain templates from birth to adulthood." NeuroImage **47, Supplement 1**: S102.

Frydecka, D., A. M. Eissa, D. H. Hewedi, M. Ali, J. Drapała, B. Misiak, E. Kłosińska, J. R. Phillips and A. A. Moustafa (2014). "Impairments of working memory in schizophrenia and bipolar disorder: the effect of history of psychotic symptoms and different aspects of cognitive task demands." Frontiers in Behavioral Neuroscience **8**: 416.

Galletly, C. A., A. C. MacFarlane and C. R. Clark (2007). "Impaired updating of working memory in schizophrenia." International Journal of Psychophysiology **63**(3): 265-274.

Gazzaley, A. and A. C. Nobre (2012). "Top-down modulation: Bridging selective attention and working memory." Trends in cognitive sciences **16**(2): 129-135.

Gazzaley, A., J. Rissman and M. D'esposito (2004). "Functional connectivity during working memory maintenance." Cognitive, Affective, & Behavioral Neuroscience **4**(4): 580-599.

Giersch, A., M. van Assche, R. L. Capa, C. Marrer and D. Gounot (2012). "Patients with Schizophrenia Do Not Preserve Automatic Grouping When Mentally Re-Grouping Figures: Shedding Light on an Ignored Difficulty." Frontiers in Psychology **3**: 274.

Glahn, D. C., J. Barrett, C. E. Bearden, J. Mintz, M. F. Green, E. S. Monkul, P. Najt, J. C. Soares and D. I. Velligan (2006). "Dissociable mechanisms for memory impairment in bipolar disorder and schizophrenia." Psychological medicine **36**(08): 1085-1095.

Glahn, D. C., J. Kim, M. S. Cohen, V. P. Poutanen, S. Therman, S. Bava, T. G. M. Van Erp, M. Manninen, M. Huttunen, J. Lönnqvist, C. G. Standertskjöld-Nordenstam and T. D. Cannon (2002). "Maintenance and Manipulation in Spatial Working Memory: Dissociations in the Prefrontal Cortex." NeuroImage **17**(1): 201-213.

Goeree, R., F. Farahati, N. Burke, G. Blackhouse, D. O'Reilly, J. Pyne and J. E. Tarride (2005). "The economic burden of schizophrenia in Canada in 2004." Current Medical Research and Opinion **21**(12): 2017-2028.

Gogtay, N., J. N. Giedd, L. Lusk, K. M. Hayashi, D. Greenstein, A. C. Vaituzis, T. F. Nugent, D. H. Herman, L. S. Clasen, A. W. Toga, J. L. Rapoport and P. M. Thompson (2004). "Dynamic mapping of human cortical development during childhood through early adulthood." Proceedings of the National Academy of Sciences of the United States of America **101**(21): 8174-8179.

Gogtay, N., D. Greenstein, M. Lenane, L. Clasen, W. Sharp, P. Gochman, P. Butler, A. Evans and J. Rapoport (2007). "Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia." Archives of general psychiatry **64**(7): 772-780.

Gold, J. M., C. M. Wilk, R. P. McMahon, R. W. Buchanan and S. J. Luck (2003). "Working memory for visual features and conjunctions in schizophrenia." Journal of abnormal psychology **112**(1): 61.

Goldman, A. L., L. Pezawas, P. Doz, V. S. Mattay, B. Fischl, B. A. Verchinski, Q. Chen, D. R. Weinberger and A. Meyer-Lindenberg (2009). "Widespread Reductions of Cortical Thickness in Schizophrenia and Spectrum Disorders and Evidence of Heritability." Archives of general psychiatry **66**(5): 467-477.

Good, C. D., I. Johnsrude, J. Ashburner, R. N. A. Henson, K. J. Friston and R. S. J. Frackowiak (2001). "Cerebral Asymmetry and the Effects of Sex and Handedness on Brain Structure: A Voxel-Based Morphometric Analysis of 465 Normal Adult Human Brains." NeuroImage **14**(3): 685-700.

Gotts, S. J., H. J. Jo, G. L. Wallace, Z. S. Saad, R. W. Cox and A. Martin (2013). "Two distinct forms of functional lateralization in the human brain." Proceedings of the National Academy of Sciences of the United States of America **110**(36): E3435-E3444.

Gray, B. E., B. Hahn, B. Robinson, A. Harvey, C. J. Leonard, S. J. Luck and J. M. Gold (2014). "Relationships Between Divided Attention and Working Memory Impairment in People With Schizophrenia." Schizophrenia Bulletin **40**(6): 1462-1471.

Green, M. F. (1996). "What are the functional consequences of neurocognitive deficit in schizophrenia?" Am J Psych **153**.

Green, M. F., R. S. Kern, D. L. Braff and J. Mintz (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the" right stuff"?, National Institute of Mental Health.

Green, M. F., R. S. Kern and R. K. Heaton (2004). "Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS." Schizophrenia Research **72**(1): 41-51.

Green, M. F., P. Satz, C. Smith and L. Nelson (1989). "Is there atypical handedness in schizophrenia?" Journal of Abnormal Psychology **98**(1): 57-61.

Greicius, M. D., K. Supekar, V. Menon and R. F. Dougherty (2008). "Resting-state functional connectivity reflects structural connectivity in the default mode network." Cerebral cortex **19**(1): 72-78.

Greve, K. W., M. C. Williams, W. G. Haas, R. R. Littell and C. Reinoso (1996). "The role of attention in Wisconsin card sorting test performance." Archives of Clinical Neuropsychology **11**(3): 215-222.

Grossman, L. S., M. Harrow, C. Rosen, R. Faull and G. P. Strauss (2008). "Sex Differences in Schizophrenia and Other Psychotic Disorders: A 20-Year Longitudinal Study of Psychosis and Recovery." Comprehensive psychiatry **49**(6): 523-529.

Grot, S., V. Petel Légaré, O. Lipp, I. Soulières, F. Dolcos and D. Luck (2017). "Abnormal prefrontal and parietal activity linked to deficient active binding in working memory in schizophrenia." Schizophrenia Research.

Grot, S., S. Potvin and D. Luck (2014). "Is there a binding deficit in working memory in patients with schizophrenia? A meta-analysis." Schizophrenia research **158**(1): 142-145.

Gsottschneider, A., Z. Keller, G. Pitschel-Walz, T. Froböse, J. Bäuml and T. Jahn (2011). "The role of encoding strategies in the verbal memory performance in patients with schizophrenia." Journal of Neuropsychology **5**(1): 56-72.

Gur, R. E. (1977). "Motoric laterality imbalance in schizophrenia: A possible concomitant of left hemisphere dysfunction." Archives of General Psychiatry **34**(1): 33-37.

Guye, M., G. J. M. Parker, M. Symms, P. Boulby, C. A. M. Wheeler-Kingshott, A. Salek-Haddadi, G. J. Barker and J. S. Duncan (2003). "Combined functional MRI and tractography to demonstrate the connectivity of the human primary motor cortex in vivo." NeuroImage **19**(4): 1349-1360.

Hahn, B., B. M. Robinson, A. N. Harvey, S. T. Kaiser, C. J. Leonard, S. J. Luck and J. M. Gold (2012). "Visuospatial Attention in Schizophrenia: Deficits in Broad Monitoring." Journal of abnormal psychology **121**(1): 119-128.

Hahn, B., B. M. Robinson, S. T. Kaiser, A. N. Harvey, V. M. Beck, C. J. Leonard, E. S. Kappenman, S. J. Luck and J. M. Gold (2010). "Failure of Schizophrenia Patients to Overcome Salient Distractors During Working Memory Encoding." Biological Psychiatry **68**(7): 603-609.

Hahn, B., B. M. Robinson, S. T. Kaiser, T. M. Matveeva, A. N. Harvey, S. J. Luck and J. M. Gold (2012). "Kraepelin and Bleuler had it right: People with schizophrenia have deficits sustaining attention over time." Journal of Abnormal Psychology **121**(3): 641-648.

Hanlon, F. M., J. M. Houck, S. D. Klimaj, A. Caprihan, A. R. Mayer, M. P. Weisend, J. R. Bustillo, D. A. Hamilton and C. D. Tesche (2012). "Fronto-temporal Anatomical Connectivity and Working-Relational Memory Performance Predict Everyday Functioning in Schizophrenia." Psychophysiology **49**(10): 1340-1352.

Hannula, D. E. and C. Ranganath (2008). "Medial Temporal Lobe Activity Predicts Successful Relational Memory Binding." The Journal of Neuroscience **28**(1): 116-124.

Hao-Yang Tan, Wei-Chieh Choo, Calvin S.L. Fones and Michael W.L. Chee (2005). "fMRI Study of Maintenance and Manipulation Processes Within Working Memory in First-Episode Schizophrenia." American Journal of Psychiatry **162**(10): 1849-1858.

Harrison, P. J. (2004). "The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications." Psychopharmacology **174**(1): 151-162.

Hartberg, C. B., G. Lawyer, H. Nyman, E. G. Jönsson, U. K. Haukvik, P. Saetre, P. S. Bjerkan, O. A. Andreassen, H. Hall and I. Agartz (2010). "Investigating relationships between cortical thickness and

cognitive performance in patients with schizophrenia and healthy adults." Psychiatry Research: Neuroimaging **182**(2): 123-133.

Health Canada (2002). "A report on Mental Illnesses in Canada." Health Canada Editorial Borad Mental Illnesses in Canada: 1-108.

Heather M. Conklin, Clayton E. Curtis, Joanna Katsanis and William G. Iacono (2000). "Verbal Working Memory Impairment in Schizophrenia Patients and Their First-Degree Relatives: Evidence From the Digit Span Task." American Journal of Psychiatry **157**(2): 275-277.

Heckers, S. (2001). "Neuroimaging studies of the hippocampus in schizophrenia." Hippocampus **11**(5): 520-528.

Heckers, S., S. Rauch, D. Goff, C. Savage, D. Schacter, A. Fischman and N. Alpert (1998). "Impaired recruitment of the hippocampus during conscious recollection in schizophrenia." Nature neuroscience **1**(4): 318-323.

Heinrichs, R. W. and K. K. Zakzanis (1998). "Neurocognitive deficit in schizophrenia, a quantitative review of the evidence." Neuropsychol **12**.

Heinrichs, R. W. and K. K. Zakzanis (1998). "Neurocognitive deficit in schizophrenia: A quantitative review of the evidence." Neuropsychology **12**(3): 426-445.

Henke, K., B. Weber, S. Kneifel, H. G. Wieser and A. Buck (1999). "Human hippocampus associates information in memory." Proceedings of the National Academy of Sciences **96**(10): 5884-5889.

Henry H. Holcomb, Adrienne C. Lahti, Deborah R. Medoff, Martin Weiler, Robert F. Dannals and Carol A. Tamminga (2000). "Brain Activation Patterns in Schizophrenic and Comparison Volunteers During a Matched-Performance Auditory Recognition Task." American Journal of Psychiatry **157**(10): 1634-1645.

Henseler, I., P. Falkai and O. Gruber (2010). "Disturbed functional connectivity within brain networks subserving domain-specific subcomponents of working memory in schizophrenia: Relation to performance and clinical symptoms." Journal of Psychiatric Research **44**(6): 364-372.

Highley, J. R., M. A. Walker, M. M. Esiri, T. J. Crow and P. J. Harrison (2002). "Asymmetry of the Uncinate Fasciculus: A Post-mortem Study of Normal Subjects and Patients with Schizophrenia." Cerebral Cortex **12**(11): 1218-1224.

Ho, B.-C., N. C. Andreasen, S. Ziebell, R. Pierson and V. Magnotta (2011). "Long-term Antipsychotic Treatment and Brain Volumes: A Longitudinal Study of First-Episode Schizophrenia." Archives of general psychiatry **68**(2): 128-137.

Hoenig, J. (1983). "The concept of Schizophrenia. Kraepelin-Bleuler-Schneider." The British Journal of Psychiatry **142**(6): 547-556.

Hoff, A. L. K., William "Neuropsychology in schizophrenia: an update." Current Opinion in Psychiatry **16**(2): 149-155.

Ian C. Wright, Sophia Rabe-Hesketh, Peter W.R. Woodruff, Anthony S. David, Robin M. Murray and Edward T. Bullmore (2000). "Meta-Analysis of Regional Brain Volumes in Schizophrenia." American Journal of Psychiatry **157**(1): 16-25.

Jablensky, A. (2010). "The diagnostic concept of schizophrenia: its history, evolution, and future prospects." Dialogues in Clinical Neuroscience **12**(3): 271-287.

Jae-Jin Kim, Jun Soo Kwon, Hae Jeong Park, Tak Youn, Do Hyung Kang, Myung Sun Kim, Dong Soo Lee and Myung Chul Lee (2003). "Functional Disconnection Between the Prefrontal and Parietal Cortices During Working Memory Processing in Schizophrenia: A [15O]H2O PET Study." American Journal of Psychiatry **160**(5): 919-923.

Jenkinson, M., C. F. Beckmann, T. E. J. Behrens, M. W. Woolrich and S. M. Smith (2012). "FSL." NeuroImage **62**(2): 782-790.

John G. Csernansky, Lei Wang, Donald Jones, Devna Rastogi-Cruz, Joel A. Posener, Gitry Heydebrand, J. Philip Miller and Michael I. Miller (2002). "Hippocampal Deformities in Schizophrenia Characterized by High Dimensional Brain Mapping." American Journal of Psychiatry **159**(12): 2000-2006.

Johnson, M. R., N. A. Morris, R. S. Astur, V. D. Calhoun, D. H. Mathalon, K. A. Kiehl and G. D. Pearlson (2006). "A functional magnetic resonance imaging study of working memory abnormalities in schizophrenia." Biological psychiatry **60**(1): 11-21.

Jonathan D. Prince , P. D., P. D. Ayse Akincigil and P. D. Evelyn Bromet (2007). "Incarceration Rates of Persons With First-Admission Psychosis." Psychiatric Services **58**(9): 1173-1180.

Jones, D. K. and M. Cercignani (2010). "Twenty-five pitfalls in the analysis of diffusion MRI data." NMR in Biomedicine **23**(7): 803-820.

Joyal, C. C., P. Hallé, D. Lapierre and S. Hodgins (2003). "Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia." Schizophrenia Research **63**(3): 297-299.

Kabani, N., G. Le Goualher, D. MacDonald and A. C. Evans (2001). "Measurement of Cortical Thickness Using an Automated 3-D Algorithm: A Validation Study." NeuroImage **13**(2): 375-380.

Karch, S., G. Leicht, I. Giegling, J. Lutz, J. Kunz, M. Buselmeier, P. Hey, A. Spörl, L. Jäger, T. Meindl, O. Pogarell, H.-J. Möller, U. Hegerl, D. Rujescu and C. Mulert (2009). "Inefficient neural activity in patients with schizophrenia and nonpsychotic relatives of schizophrenic patients: Evidence from a working memory task." Journal of Psychiatric Research **43**(15): 1185-1194.

Karlsen, P. J., R. J. Allen, A. D. Baddeley and G. J. Hitch (2010). "Binding across space and time in visual working memory." Memory & Cognition **38**(3): 292-303.

Karlsgodt, K. H., D. Sun, A. M. Jimenez, E. S. Lutkenhoff, R. Willhite, T. G. Van Erp and T. D. Cannon (2008). "Developmental disruptions in neural connectivity in the pathophysiology of schizophrenia." Development and psychopathology **20**(04): 1297-1327.

Karlsgodt, K. H., T. G. M. van Erp, R. A. Poldrack, C. E. Bearden, K. H. Nuechterlein and T. D. Cannon (2008). "Diffusion Tensor Imaging of the Superior Longitudinal Fasciculus and Working Memory in Recent-Onset Schizophrenia." Biological Psychiatry **63**(5): 512-518.

Karnik-Henry, M. S., L. Wang, D. M. Barch, M. P. Harms, C. Campanella and J. G. Csernansky (2012). "Medial temporal lobe structure and cognition in individuals with schizophrenia and in their non-psychotic siblings." Schizophrenia Research **138**(2-3): 128-135.

Karnik-Henry, M. S., L. Wang, D. M. Barch, M. P. Harms, C. Campanella and J. G. Csernansky (2012). "Medial temporal lobe structure and cognition in individuals with schizophrenia and in their non-psychotic siblings." Schizophrenia Research **138**(2–3): 128-135.

Kay, S. R., A. Flszbein and L. A. Opfer (1987). "The positive and negative syndrome scale (PANSS) for schizophrenia." Schizophrenia bulletin **13**(2): 261.

Keedy, S. K., C. L. Ebens, M. S. Keshavan and J. A. Sweeney (2006). "Functional magnetic resonance imaging studies of eye movements in first episode schizophrenia: smooth pursuit, visually guided saccades and the oculomotor delayed response task." Psychiatry Research: Neuroimaging **146**(3): 199-211.

Keefe, R. E., R. M. Bilder, S. M. Davis and et al. (2007). "Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the catie trial." Archives of General Psychiatry **64**(6): 633-647.

Keefe, R. S. E. (2014). "The Longitudinal Course of Cognitive Impairment in Schizophrenia: An Examination of Data From Premorbid Through Posttreatment Phases of Illness." The Journal of Clinical Psychiatry **75**.

Keefe, R. S. E., S. G. Silva, D. O. Perkins and J. A. Lieberman (1999). "The Effects of Atypical Antipsychotic Drugs on Neurocognitive Impairment in Schizophrenia: A Review and Meta-analysis." Schizophrenia Bulletin **25**(2): 201-222.

Kelvin O. Lim , M. D., P. D. Babak A. Ardekani , M. D. Jay Nierenberg , Ph.D. ,, P. D. Pamela D. Butler , M. D. Daniel C. Javitt , Ph.D. , and P. D. Matthew J. Hoptman (2006). "Voxelwise Correlational Analyses of White Matter Integrity in Multiple Cognitive Domains in Schizophrenia." American Journal of Psychiatry **163**(11): 2008-2010.

Kevin Blot, J. B., Satoru Otani (2013). "The effect of non-competitive NMDA receptor antagonist MK-801 on neuronal activity in rodent prefrontal cortex: an animal model for cognitive symptoms of schizophrenia." Journal of Physiology - Paris **107**: 448-451.

Kim, J., D. C. Glahn, K. H. Nuechterlein and T. D. Cannon (2004). "Maintenance and manipulation of information in schizophrenia: further evidence for impairment in the central executive component of working memory." Schizophrenia Research **68**(2–3): 173-187.

Kim, J., N. L. Matthews and S. Park (2010). "An event-related FMRI study of phonological verbal working memory in schizophrenia." PloS one **5**(8): e12068.

Kim, J., S. Park, Y.-W. Shin, K. J. Lee and J. S. Kwon (2006). "Self-initiated encoding facilitates object working memory in schizophrenia: implications for the etiology of working memory deficit." Schizophrenia research **82**(1): 65-74.

Kim, J. S., V. Singh, J. K. Lee, J. Lerch, Y. Ad-Dab'bagh, D. MacDonald, J. M. Lee, S. I. Kim and A. C. Evans (2005). "Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification." NeuroImage **27**(1): 210-221.

Kim, M.-S., Y. Namgoong and T. Youn (2008). "Effect of organizational strategy on visual memory in patients with schizophrenia." Psychiatry and Clinical Neurosciences **62**(4): 427-434.

Kingsley, P. B. and W. G. Monahan (2004). "Selection of the optimum b factor for diffusion-weighted magnetic resonance imaging assessment of ischemic stroke." Magnetic resonance in medicine **51**(5): 996-1001.

Klauer, K. C. and Z. Zhao (2004). "Double Dissociations in Visual and Spatial Short-Term Memory." Journal of Experimental Psychology: General **133**(3): 355-381.

Knecht, S., B. Dräger, M. Deppe, L. Bobe, H. Lohmann, A. Flöel, E. B. Ringelstein and H. Henningsen (2000). "Handedness and hemispheric language dominance in healthy humans." Brain **123**(12): 2512-2518.

Knöchel, C., L. O'Dwyer, G. Alves, B. Reinke, J. Magerkurth, A. Rotarska-Jagiela, D. Prvulovic, H. Hampel, D. E. J. Linden and V. Oertel-Knöchel (2012). "Association between white matter fiber integrity

and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives." Schizophrenia Research **140**(1–3): 129-135.

Koechlin, E., C. Ody and F. Kouneiher (2003). "The Architecture of Cognitive Control in the Human Prefrontal Cortex." Science **302**(5648): 1181-1185.

Kraepelin, E. (1971). Dementia praecox and paraphrenia, Krieger Publishing Company.

Kreither, J., J. Lopez-Calderon, C. J. Leonard, B. M. Robinson, A. Ruffle, B. Hahn, J. M. Gold and S. J. Luck (2017). "Electrophysiological Evidence for Hyperfocusing of Spatial Attention in Schizophrenia." The Journal of Neuroscience.

Kremen, W. S., L. J. Seidman, S. V. Faraone and M. T. Tsuang (2001). "Intelligence quotient and neuropsychological profiles in patients with schizophrenia and in normal volunteers." Biological Psychiatry **50**(6): 453-462.

Kremen, W. S., S. Vinogradov, J. H. Poole, C. A. Schaefer, R. F. Deicken, P. Factor-Litvak and A. S. Brown (2010). "Cognitive Decline in Schizophrenia from Childhood to Midlife: A 33-Year Longitudinal Birth Cohort Study." Schizophrenia research **118**(1-3): 1-5.

Kubicki, M., R. McCarley, C.-F. Westin, H.-J. Park, S. Maier, R. Kikinis, F. A. Jolesz and M. E. Shenton (2007). "A review of diffusion tensor imaging studies in schizophrenia." Journal of psychiatric research **41**(1): 15-30.

Kubicki, M., C.-F. Westin, S. E. Maier, M. Frumin, P. G. Nestor, D. F. Salisbury, R. Kikinis, F. A. Jolesz, R. W. McCarley and M. E. Shenton (2002). "Uncinate Fasciculus Findings in Schizophrenia: A Magnetic Resonance Diffusion Tensor Imaging Study." The American journal of psychiatry **159**(5): 813-820.

Kuperberg, G. R., M. R. Broome, P. K. McGuire, A. S. David, M. Eddy, F. Ozawa, D. Goff, W. C. West, S. C. Williams and A. J. van der Kouwe (2003). "Regionally localized thinning of the cerebral cortex in schizophrenia." Archives of general psychiatry **60**(9): 878-888.

Kyriakopoulos, M., T. Bargiotas, G. J. Barker and S. Frangou (2008). "Diffusion tensor imaging in schizophrenia." European Psychiatry **23**(4): 255-273.

Lebel, C., M. Gee, R. Camicioli, M. Wieler, W. Martin and C. Beaulieu (2012). "Diffusion tensor imaging of white matter tract evolution over the lifespan." NeuroImage **60**(1): 340-352.

Lebel, C., L. Walker, A. Leemans, L. Phillips and C. Beaulieu (2008). "Microstructural maturation of the human brain from childhood to adulthood." NeuroImage **40**(3): 1044-1055.

Lee, J., B. S. Folley, J. Gore and S. Park (2008). "Origins of spatial working memory deficits in schizophrenia: an event-related FMRI and near-infrared spectroscopy study." PloS one **3**(3): e1760.

Lee, J. and S. Park (2005). "Working Memory Impairments in Schizophrenia: A Meta-Analysis." Journal of Abnormal Psychology **114**(4): 599-611.

Lee, J. and S. Park (2005). "Working Memory Impairments in Schizophrenia: A Meta-Analysis. ." Journal of Abnormal Psychology, **114**(4): 599-911.

Leiderman, E. A. and S. A. Strejilevich (2004). "Visuospatial deficits in schizophrenia: central executive and memory subsystems impairments." Schizophrenia Research **68**(2–3): 217-223.

Lepage, M., R. Habib, H. Cormier, S. Houle and A. R. McIntosh (2000). "Neural correlates of semantic associative encoding in episodic memory." Cognitive Brain Research **9**(3): 271-280.

Lerch, J. P. and A. C. Evans (2005). "Cortical thickness analysis examined through power analysis and a population simulation." Neuroimage **24**(1): 163-173.

Lesh, T. A., T. A. Niendam, M. J. Minzenberg and C. S. Carter (2011). "Cognitive Control Deficits in Schizophrenia: Mechanisms and Meaning." Neuropsychopharmacology **36**(1): 316-338.

Lett, T. A., A. N. Voineskos, J. L. Kennedy, B. Levine and Z. J. Daskalakis (2014). "Treating Working Memory Deficits in Schizophrenia: A Review of the Neurobiology." Biological Psychiatry **75**(5): 361-370.

Leung, H. C., J. C. Gore and P. S. Goldman-Rakic (2002). "Sustained Mnemonic Response in the Human Middle Frontal Gyrus during On-Line Storage of Spatial Memoranda." Journal of Cognitive Neuroscience **14**(4): 659-671.

Levitt, J. J., L. Bobrow, D. Lucia and P. Srinivasan (2010). A selective review of volumetric and morphometric imaging in schizophrenia. Behavioral Neurobiology of Schizophrenia and Its Treatment, Springer**:** 243-281.

Luck, D., L. Buchy, M. Lepage and J.-M. Danion (2009). "Examining the effects of two factors on working memory maintenance of bound information in schizophrenia." Journal of the International Neuropsychological Society **15**(04): 597-605.

Luck, D., J.-M. Danion, C. Marrer, B.-T. Pham, D. Gounot and J. Foucher (2010). "Abnormal medial temporal activity for bound information during working memory maintenance in patients with schizophrenia." Hippocampus **20**(8): 936-948.

Luck, D., J.-M. Danion, C. Marrer, B.-T. Pham, D. Gounot and J. Foucher (2010). "The right parahippocampal gyrus contributes to the formation and maintenance of bound information in working memory." Brain and Cognition **72**(2): 255-263.

Luck, D., J. R. Foucher, I. Offerlin-Meyer, M. Lepage and J.-M. Danion (2008). "Assessment of single and bound features in a working memory task in schizophrenia." Schizophrenia Research **100**(1–3): 153-160.

Luck, S. J. and J. M. Gold (2008). "The Construct of Attention in Schizophrenia." Biological psychiatry **64**(1): 34-39.

Luck, S. J. and E. K. Vogel (1997). "The capacity of visual working memory for features and conjunctions." Nature **390**(6657): 279-281.

Luck, S. J. and E. K. Vogel (2013). "Visual Working Memory Capacity: From Psychophysics and Neurobiology to Individual Differences." Trends in cognitive sciences **17**(8): 391-400.

Luders, E., K. L. Narr, P. M. Thompson, D. E. Rex, L. Jancke and A. W. Toga (2006). "Hemispheric Asymmetries in Cortical Thickness." Cerebral Cortex **16**(8): 1232-1238.

Luoma, S., H. Hakko, T. Ollinen, M. R. Järvelin and S. Lindeman (2008). "Association between age at onset and clinical features of schizophrenia: The Northern Finland 1966 birth cohort study." European Psychiatry **23**(5): 331-335.

Lyle, K. B., S. M. Bloise and M. K. Johnson (2006). "Age-related binding deficits and the content of false memories." Psychology and Aging **21**(1): 86-95.

Lynn, P. A., S. S. Kang and S. R. Sponheim (2016). "Impaired retrieval processes evident during visual working memory in schizophrenia." Schizophrenia Research: Cognition **5**: 47-55.

Lyttelton, O. C., S. Karama, Y. Ad-Dab'bagh, R. J. Zatorre, F. Carbonell, K. Worsley and A. C. Evans (2009). "Positional and surface area asymmetry of the human cerebral cortex." NeuroImage **46**(4): 895-903.

MacDonald, D., N. Kabani, D. Avis and A. C. Evans (2000). "Automated 3-D Extraction of Inner and Outer Surfaces of Cerebral Cortex from MRI." NeuroImage **12**(3): 340-356.

Macmillan, N. A. and C. D. Creelman (1990). "Response bias: Characteristics of detection theory, threshold theory, and "nonparametric" indexes." Psychological Bulletin **107**(3): 401-413.

Magliano, L., A. Fiorillo, C. De Rosa, C. Malangone and M. Maj (2005). "Family burden in long-term diseases: A comparative study in schizophrenia vs. physical disorders." Social Science and Medicine **61**(2): 313-322.

Makowski, C., M. Bodnar, A. K. Malla, R. Joober and M. Lepage (2016). "Age-related cortical thickness trajectories in first episode psychosis patients presenting with early persistent negative symptoms." NPJ Schizophrenia **2**: 16029.

Makris, N., D. N. Kennedy, S. McInerney, A. G. Sorensen, R. Wang, V. S. Caviness and D. N. Pandya (2005). "Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study." Cerebral cortex **15**(6): 854-869.

Mather, M. (2007). "Emotional arousal and memory binding: An object-based framework." Perspectives on Psychological Science **2**(1): 33-52.

Mayer, J. S., K. Fukuda, E. K. Vogel and S. Park (2012). "Impaired contingent attentional capture predicts reduced working memory capacity in schizophrenia." PloS one **7**(11): e48586.

Mayer, J. S. and S. Park (2012). "Working memory encoding and false memory in schizophrenia and bipolar disorder in a spatial delayed response task." Journal of abnormal psychology **121**(3): 784.

McCleery, A., J. Addington and D. Addington (2006). "Substance misuse and cognitive functioning in early psychosis: A 2 year follow-up." Schizophrenia Research **88**(1–3): 187-191.

McClure, M. M., M. J. Romero, C. R. Bowie, A. Reichenberg, P. D. Harvey and L. J. Siever (2007). "Visual-spatial learning and memory in schizotypal personality disorder: Continued evidence for the importance of working memory in the schizophrenia spectrum." Archives of Clinical Neuropsychology **22**(1): 109-116.

McIntosh, A. M., S. M. Maniega, G. K. S. Lymer, J. McKirdy, J. Hall, J. E. D. Sussmann, M. E. Bastin, J. D. Clayden, E. C. Johnstone and S. M. Lawrie (2008). "White Matter Tractography in Bipolar Disorder and Schizophrenia." Biological Psychiatry **64**(12): 1088-1092.

Meda, S. A., M. C. Stevens, B. S. Folley, V. D. Calhoun and G. D. Pearlson (2009). "Evidence for Anomalous Network Connectivity during Working Memory Encoding in Schizophrenia: An ICA Based Analysis." PLOS ONE **4**(11): e7911.

Meltzer, J. A. and R. T. Constable (2005). "Activation of human hippocampal formation reflects success in both encoding and cued recall of paired associates." Neuroimage **24**(2): 384-397.

Meyer-Lindenberg, A. S., R. K. Olsen, P. D. Kohn and et al. (2005). "Regionally specific disturbance of dorsolateral prefrontal–hippocampal functional connectivity in schizophrenia." Archives of General Psychiatry **62**(4): 379-386.

Meyer-Lindenberg, A. S., Olsen, R. K.,Kohn, P. D. et al., (2005). "Regionally specific disturbance of dorsolateral prefrontal–hippocampal functional connectivity in schizophrenia." Archives of General Psychiatry **62**(4): 379-386.

Michael Foster, G. (1996). "What are the functional consequences of neurocognitive deficits in schizophrenia?" American Journal of Psychiatry **153**(3): 321-330.

Miller, E. K., Cohen, Jonathan D. (2001). "An Integrative Theory of Prefrontal Cortex Function " Annual Review of Neuroscience **24**(1): 167-202.

Mishara, A. L. and T. E. Goldberg (2004). "A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book." Biological Psychiatry **55**(10): 1013-1022.

Mitchell, K. J., M. K. Johnson, C. L. Raye and M. D'Esposito (2000). "fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory1." Cognitive Brain Research **10**(1–2): 197-206.

Mitchell, R. L. C. and T. J. Crow (2005). "Right hemisphere language functions and schizophrenia: the forgotten hemisphere?" Brain **128**(5): 963-978.

Mohn, C., K. Sundet and B. R. Rund (2014). "The relationship between IQ and performance on the MATRICS Consensus Cognitive Battery." Schizophrenia Research: Cognition **1**(2): 96-100.

Moncrieff, J. and J. Leo (2010). "A systematic review of the effects of antipsychotic drugs on brain volume." Psychological Medicine **40**(9): 1409-1422.

Morey, C. C. (2011). "Maintaining binding in working memory: Comparing the effects of intentional goals and incidental affordances." Consciousness and Cognition **20**(3): 920-927.

Morice, R. and A. Delahunty (1996). "Frontal/executive impairments in schizophrenia." schizophrenia Bulletin **22**(1): 125-137.

Morris, R., T. Rushe, P. Woodruffe and R. Murray (1995). "Problem solving in schizophrenia: a specific deficit in planning ability." Schizophrenia research **14**(3): 235-246.

Müller, N. G. and R. T. Knight (2006). "The functional neuroanatomy of working memory: Contributions of human brain lesion studies." Neuroscience **139**(1): 51-58.

Munetz, M. R., T. P. Grande and M. R. Chambers (2001). "The incarceration of individuals with severe mental disorders." Community mental health journal **37**(4): 361-372.

Narr, K. L., R. M. Bilder, A. W. Toga, R. P. Woods, D. E. Rex, P. R. Szeszko, D. Robinson, S. Sevy, H. Gunduz-Bruce and Y.-P. Wang (2005). "Mapping cortical thickness and gray matter concentration in first episode schizophrenia." Cerebral cortex **15**(6): 708-719.

Narum, S. R. (2006). "Beyond Bonferroni: less conservative analyses for conservation genetics." Conservation genetics **7**(5): 783-787.

National Institute of Mental Health. (2015). "NIMH Strategic Plan for Research ".

Nelson, M. D., A. J. Saykin, L. A. Flashman and H. J. Riordan (1998). "Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study." Archives of general psychiatry **55**(5): 433-440.

Nestor, P. G., M. Kubicki, R. J. Gurrera, M. Niznikiewicz, M. Frumin, R. W. McCarley and M. E. Shenton (2004). "Neuropsychological Correlates of Diffusion Tensor Imaging in Schizophrenia." Neuropsychology **18**(4): 629-637.

Nestor, P. G., M. Kubicki, M. Niznikiewicz, R. J. Gurrera, R. W. McCarley and M. E. Shenton (2008). "Neuropsychological Disturbance in Schizophrenia: A Diffusion Tensor Imaging Study." Neuropsychology **22**(2): 246-254.

Niznikiewicz, M., R. Donnino, R. W. McCarley, P. G. Nestor, D. V. Iosifescu, B. O'Donnell, J. Levitt and M. E. Shenton (2000). "Abnormal angular gyrus asymmetry in schizophrenia." American Journal of Psychiatry **157**(3): 428-437.

Nuechterlein, K. H., D. M. Barch, J. M. Gold, T. E. Goldberg, M. F. Green and R. K. Heaton (2004). "Identification of separable cognitive factors in schizophrenia." Schizophrenia Research **72**(1): 29-39.

Olesen, P. J., Z. Nagy, H. Westerberg and T. Klingberg (2003). "Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network." Cognitive Brain Research **18**(1): 48-57.

Olsen, R. K., S. N. Moses, L. Riggs and J. D. Ryan (2012). "The hippocampus supports multiple cognitive processes through relational binding and comparison." Frontiers in Human Neuroscience **6**: 146.

Olson, I. R., R. J. V. D. Heide, K. H. Alm and G. Vyas (2015). "Development of the uncinate fasciculus: Implications for theory and developmental disorders." Developmental Cognitive Neuroscience **14**: 50-61.

Olson, I. R., K. S. Moore, M. Stark and A. Chatterjee (2006). "Visual Working Memory Is Impaired when the Medial Temporal Lobe Is Damaged." Journal of Cognitive Neuroscience **18**(7): 1087-1097.

Opitz, B., A. Mecklinger and A. D. Friederici (2000). "Functional Asymmetry of Human Prefrontal Cortex: Encoding and Retrieval of Verbally and Nonverbally Coded Information." Learning & Memory **7**(2): 85-96.

Oram, J., G. M. Geffen, L. B. Geffen, D. J. Kavanagh and J. J. McGrath (2005). "Executive control of working memory in schizophrenia." Psychiatry Research **135**(2): 81-90.

Orellana, G. and A. Slachevsky (2013). "Executive Functioning in Schizophrenia." Frontiers in Psychiatry **4**: 35.

Owen, A. M., A. C. Evans and M. Petrides (1996). "Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study." Cerebral Cortex **6**(1): 31-38.

Owen, A. M., K. M. McMillan, A. R. Laird and E. Bullmore (2005). "N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies." Human Brain Mapping **25**(1): 46-59.

Palmer, B. W., R. K. Heaton, J. S. Paulsen, J. Kuck, D. Braff, M. J. Harris, S. Zisook and D. V. Jeste (1997). "Is it possible to be schizophrenic yet neuropsychologically normal?" Neuropsychology **11**(3): 437-446.

Pantelis, C., F. Z. Barber, T. R. E. Barnes, H. E. Nelson, A. M. Owen and T. W. Robbins (1999). "Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage." Schizophrenia Research **37**(3): 251-270.

Park, S. and D. C. Gooding (2014). "Working memory impairment as an endophenotypic marker of a schizophrenia diathesis." Schizophrenia Research: Cognition **1**(3): 127-136.

Park, S. and P. S. Holzman (1992). "Schizophrenics show spatial working memory deficits." Archives of General Psychiatry **49**(12): 975-982.

Pérez-Iglesias, R., D. Tordesillas-Gutiérrez, G. J. Barker, P. K. McGuire, R. Roiz-Santiañez, I. Mata, E. M. de Lucas, F. Quintana, J. L. Vazquez-Barquero and B. Crespo-Facorro (2010). "White matter defects in first episode psychosis patients: a voxelwise analysis of diffusion tensor imaging." Neuroimage **49**(1): 199-204.

Peters, B. D., N. Schmitz, P. M. Dingemans, T. A. van Amelsvoort, D. H. Linszen, L. de Haan, C. B. Majoie and G. J. den Heeten (2009). "Preliminary evidence for reduced frontal white matter integrity in subjects at ultra-high-risk for psychosis." Schizophrenia Research **111**(1–3): 192-193.

Petrides, M. and D. N. Pandya (2002). "Association pathways of the prefrontal cortex and functional observations." Principles of frontal lobe function **1**: 31-50.

Piekema, C., R. P. C. Kessels, R. B. Mars, K. M. Petersson and G. Fernández (2006). "The right hippocampus participates in short-term memory maintenance of object–location associations." NeuroImage **33**(1): 374-382.

Pilgrim, B. M., J. E. Meyers, J. Bayless and M. M. Whetstone (1999). "Validity of the Ward seven-subtest WAIS-III short form in a neuropsychological population." Applied Neuropsychology **6**(4): 243-246.

Plessen, K. J., K. Hugdahl, R. Bansal, X. Hao and B. S. Peterson (2014). "Sex, Age, and Cognitive Correlates of Asymmetries in Thickness of the Cortical Mantle Across the Life Span." The Journal of Neuroscience **34**(18): 6294-6302.

Potvin, S., C. C. Joyal, J. Pelletier and E. Stip (2008). "Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis." Schizophrenia Research **100**(1–3): 242-251.

Potvin, S., T. Pampoulova, O. Lipp, L. Aït Bentaleb, P. Lalonde and E. Stip (2008). "Working memory and depressive symptoms in patients with schizophrenia and substance use disorders." Cognitive Neuropsychiatry **13**(4): 357-366.

Powell, H. W. R., G. J. M. Parker, D. C. Alexander, M. R. Symms, P. A. Boulby, C. A. M. Wheeler-Kingshott, G. J. Barker, U. Noppeney, M. J. Koepp and J. S. Duncan (2006). "Hemispheric asymmetries in language-related pathways: A combined functional MRI and tractography study." NeuroImage **32**(1): 388-399.

Prabhakaran, V., K. Narayanan, Z. Zhao and J. Gabrieli (2000). "Integration of diverse information in working memory within the frontal lobe." Nature neuroscience **3**(1): 85-90.

Price, G., M. Cercignani, G. J. M. Parker, D. R. Altmann, T. R. E. Barnes, G. J. Barker, E. M. Joyce and M. A. Ron (2008). "White matter tracts in first-episode psychosis: A DTI tractography study of the uncinate fasciculus." Neuroimage **39**(3): 949-955.

Quak, M., R. E. London and D. Talsma (2015). "A multisensory perspective of working memory." Frontiers in Human Neuroscience **9**: 197.

Ragland, J. D., A. R. Laird, C. Ranganath, R. S. Blumenfeld, S. M. Gonzales and D. C. Glahn (2009). "Prefrontal Activation Deficits During Episodic Memory in Schizophrenia." The American journal of psychiatry **166**(8): 863-874.

Ragland, J. D., C. Ranganath, J. Phillips, M. A. Boudewyn, A. M. Kring, T. A. Lesh, D. L. Long, S. J. Luck, T. A. Niendam, M. Solomon, T. Y. Swaab and C. S. Carter (2015). "Cognitive Control of Episodic

Memory in Schizophrenia: Differential Role of Dorsolateral and Ventrolateral Prefrontal Cortex." Frontiers in Human Neuroscience **9**: 604.

Rapoport, J. L., A. M. Addington, S. Frangou and M. Psych (2005). The neurodevelopmental model of schizophrenia: update 2005, Nature Publishing Group.

Read, J., N. Haslam, L. Sayce and E. Davies (2006). "Prejudice and schizophrenia: a review of the 'mental illness is an illness like any other' approach." Acta Psychiatrica Scandinavica **114**(5): 303-318.

Ribolsi, M., Z. J. Daskalakis, A. Siracusano and G. Koch (2014). "Abnormal asymmetry of brain connectivity in Schizophrenia." Frontiers in Human Neuroscience **8**.

Riggs, L., S. N. Moses, T. Bardouille, A. T. Herdman, B. Ross and J. D. Ryan (2009). "A complementary analytic approach to examining medial temporal lobe sources using magnetoencephalography." NeuroImage **45**(2): 627-642.

Robert Rosenheck, Douglas Leslie, Richard Keefe, Joseph McEvoy, Marvin Swartz, Diana Perkins, Scott Stroup, John K. Hsiao, Jeffrey Lieberman and CATIE Study Investigators Group (2006). "Barriers to Employment for People With Schizophrenia." American Journal of Psychiatry **163**(3): 411-417.

Rottschy, C., R. Langner, I. Dogan, K. Reetz, A. R. Laird, J. B. Schulz, P. T. Fox and S. B. Eickhoff (2012). "Modelling neural correlates of working memory: A coordinate-based meta-analysis." NeuroImage **60**(1): 830-846.

Sakurai, T., N. J. Gamo, T. Hikida, S.-H. Kim, T. Murai, T. Tomoda and A. Sawa (2015). "Converging models of schizophrenia – Network alterations of prefrontal cortex underlying cognitive impairments." Progress in Neurobiology **134**: 178-201.

Salamé, P., F. Burglen and J.-M. Danion (2006). "Differential disruptions of working memory components in schizophrenia in an object–location binding task using the suppression paradigm." Journal of the International Neuropsychological Society **12**(04): 510-518.

Sanfilipo, M., T. Lafargue, H. Rusinek, L. Arena, C. Loneragan, A. Lautin, J. Rotrosen and A. Wolkin (2002). "Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms." Psychiatry Research: Neuroimaging **116**(1–2): 1-23.

Sasamoto, A., J. Miyata, M. Kubota, K. Hirao, R. Kawada, S. Fujimoto, Y. Tanaka, M. Hazama, G. Sugihara, N. Sawamoto, H. Fukuyama, H. Takahashi and T. Murai (2014). "Global Association Between Cortical Thinning and White Matter Integrity Reduction in Schizophrenia." Schizophrenia Bulletin **40**(2): 420-427.

Schlaug, G., S. Marchina and A. Norton (2009). "Evidence for Plasticity in White Matter Tracts of Chronic Aphasic Patients Undergoing Intense Intonation-based Speech Therapy." Annals of the New York Academy of Sciences **1169**: 385-394.

Schlösser, R. G. M., K. Koch, G. Wagner, I. Nenadic, M. Roebel, C. Schachtzabel, M. Axer, C. Schultz, J. R. Reichenbach and H. Sauer (2008). "Inefficient executive cognitive control in schizophrenia is preceded by altered functional activation during information encoding: An fMRI study." Neuropsychologia **46**(1): 336-347.

Schneider, F., U. Habel, M. Reske, T. Kellermann, T. Stöcker, N. J. Shah, K. Zilles, D. F. Braus, A. Schmitt, R. Schlösser, M. Wagner, I. Frommann, T. Kircher, A. Rapp, E. Meisenzahl, S. Ufer, S. Ruhrmann, R. Thienel, H. Sauer, F. A. Henn and W. Gaebel (2007). "Neural correlates of working memory dysfunction in first-episode schizophrenia patients: An fMRI multi-center study." Schizophrenia Research **89**(1–3): 198-210.

Schneider, K. (1950). "Klinische Psychopathologie." **8th edition**.

Schultz, C. C., K. Koch, G. Wagner, M. Roebel, C. Schachtzabel, C. Gaser, I. Nenadic, J. R. Reichenbach, H. Sauer and R. G. M. Schlösser (2010). "Reduced cortical thickness in first episode schizophrenia." Schizophrenia Research **116**(2–3): 204-209.

Seidman, L. J., M. Lanca, W. S. Kremen, S. V. Faraone and M. T. Tsuang (2003). "Organizational and visual memory deficits in schizophrenia and bipolar psychoses using the Rey-Osterrieth complex figure: effects of duration of illness." Journal of Clinical and Experimental Neuropsychology **25**(7): 949-964.

Sharma, A., M. Weisbrod, S. Kaiser, J. Markela-Lerenc and S. Bender (2011). "Deficits in fronto-posterior interactions point to inefficient resource allocation in schizophrenia." Acta Psychiatrica Scandinavica **123**(2): 125-135.

Skelley, S. L., T. E. Goldberg, M. F. Egan, D. R. Weinberger and J. M. Gold (2008). "Verbal and visual memory: Characterizing the clinical and intermediate phenotype in schizophrenia." Schizophrenia Research **105**(1–3): 78-85.

Sled, J. G., A. P. Zijdenbos and A. C. Evans (1998). "A nonparametric method for automatic correction of intensity nonuniformity in MRI data." IEEE Transactions on Medical Imaging **17**(1): 87-97.

Smith, E. E., T. S. Eich, D. Cebenoyan and C. Malapani (2011). "Intact and impaired cognitive-control processes in schizophrenia." Schizophrenia research **126**(1): 132-137.

Smith, E. E. and J. Jonides (1999). "Storage and executive processes in the frontal lobes." Science **283**(5408): 1657-1661.

Smith, S. M. (2002). "Fast robust automated brain extraction." Human brain mapping **17**(3): 143-155.

Smith, S. M., M. Jenkinson, M. W. Woolrich, C. F. Beckmann, T. E. J. Behrens, H. Johansen-Berg, P. R. Bannister, M. De Luca, I. Drobnjak, D. E. Flitney, R. K. Niazy, J. Saunders, J. Vickers, Y. Zhang, N. De Stefano, J. M. Brady and P. M. Matthews (2004). "Advances in functional and structural MR image analysis and implementation as FSL." NeuroImage **23, Supplement 1**: S208-S219.

Snodgrass, J. G. and J. Corwin (1988). "Pragmatics of measuring recognition memory: applications to dementia and amnesia." Journal of Experimental Psychology: General **117**(1): 34.

Sommer, T., M. Rose, J. Gläscher, T. Wolbers and C. Büchel (2005). "Dissociable contributions within the medial temporal lobe to encoding of object-location associations." Learning & Memory **12**(3): 343-351.

Spence, S. A., P. M. Grasby, P. F. Liddle, M. D. Stefan, T. Sharma, R. M. Murray, J. S. E. Hellewell, K. J. Friston, C. D. Frith, S. R. Hirsch and J. F. W. Deakin (2000). "Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk." Focal dysfunction and distributed disconnectivity reappraised **176**(1): 52-60.

Sperling, R., E. Chua, A. Cocchiarella, E. Rand-Giovannetti, R. Poldrack, D. L. Schacter and M. Albert (2003). "Putting names to faces:: Successful encoding of associative memories activates the anterior hippocampal formation." Neuroimage **20**(2): 1400-1410.

Spindler, K. A., E. V. Sullivan, V. Menon, K. O. Lim and A. Pfefferbaum (1997). "Deficits in multiple systems of working memory in schizophrenia." Schizophrenia Research **27**(1): 1-10.

Spoletini, I., A. Cherubini, M. Di Paola, G. Banfi, N. Rüsch, G. Martinotti, P. Bria, I. A. Rubino, A. Siracusano, C. Caltagirone and G. Spalletta (2009). "Reduced fronto-temporal connectivity is associated

with frontal gray matter density reduction and neuropsychological deficit in schizophrenia." Schizophrenia Research **108**(1–3): 57-68.

Strauss, J. S. C., W.T.; Bartko, J.J. (1974). "An approach to the diagnosis and understanding of schizophrenia: Part III. Speculations on the processes that underlie schizophrenic symptoms and signs." Schizophr. Bull. **11**: 61-75.

Talsma, D. (2015). "Predictive coding and multisensory integration: an attentional account of the multisensory mind." Frontiers in integrative neuroscience **9**: 19.

Tamminga, C. A. and H. H. Holcomb (2004). "Phenotype of schizophrenia: a review and formulation." Mol Psychiatry **10**(1): 27-39.

Tandon, R., H. A. Nasrallah and M. S. Keshavan (2009). "Schizophrenia, “just the facts” 4. Clinical features and conceptualization." Schizophrenia Research **110**(1–3): 1-23.

Tandon, R., H. A. Nasrallah and M. S. Keshavan (2010). "Schizophrenia, “Just the Facts” 5. Treatment and prevention Past, present, and future." Schizophrenia Research **122**(1–3): 1-23.

Taoka, T., M. Morikawa, T. Akashi, T. Miyasaka, H. Nakagawa, K. Kiuchi, T. Kishimoto and K. Kichikawa (2009). "Fractional Anisotropy–Threshold Dependence in Tract-Based Diffusion Tensor Analysis: Evaluation of the Uncinate Fasciculus in Alzheimer Disease." American Journal of Neuroradiology **30**(9): 1700-1703.

Tek, C., J. Gold, T. Blaxton, C. Wilk, R. P. McMahon and R. W. Buchanan (2002). "Visual perceptual and working memory impairments in schizophrenia." Archives of general psychiatry **59**(2): 146-153.

Thomas, B., M. Eyssen, R. Peeters, G. Molenaers, P. Van Hecke, P. De Cock and S. Sunaert (2005). "Quantitative diffusion tensor imaging in cerebral palsy due to periventricular white matter injury." Brain **128**(11): 2562-2577.

Thompson, P. M., C. Vidal, J. N. Giedd, P. Gochman, J. Blumenthal, R. Nicolson, A. W. Toga and J. L. Rapoport (2001). "Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia." Proceedings of the National Academy of Sciences of the United States of America **98**(20): 11650-11655.

Todd, J. J. and R. Marois (2004). "Capacity limit of visual short-term memory in human posterior parietal cortex." Nature **428**(6984): 751-754.

Toga, A. W. and P. M. Thompson (2003). "Mapping brain asymmetry." Nat Rev Neurosci **4**(1): 37-48.

Tohka, J., A. Zijdenbos and A. Evans (2004). "Fast and robust parameter estimation for statistical partial volume models in brain MRI." NeuroImage **23**(1): 84-97.

Toulopoulou, T., M. Picchioni, F. Rijsdijk and et al. (2007). "Substantial genetic overlap between neurocognition and schizophrenia: Genetic modeling in twin samples." Archives of General Psychiatry **64**(12): 1348-1355.

Toulopoulou, T., S. Rabe-Hesketh, H. King, R. M. Murray and R. G. Morris (2003). "Episodic memory in schizophrenic patients and their relatives." Schizophrenia Research **63**(3): 261-271.

Toulopoulouand, T. and R. M. Murray (2004). "Verbal memory deficit in patients with schizophrenia: an important future target for treatment." Expert Review of Neurotherapeutics **4**(1): 43-52.

Toussaint, N., J.-C. Souplet and P. Fillard (2007). MedINRIA: medical image navigation and research tool by INRIA. Proc. of MICCAI.

Tresch, M. C., H. M. Sinnamon and J. G. Seamon (1993). "Double dissociation of spatial and object visual memory: Evidence from selective interference in intact human subjects." Neuropsychologia **31**(3): 211-219.

Trotta, A., Murray, R., & MacCabe, J. (2015). "Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis." Psychological Medicine **45**(2): 381-394.

van den Heuvel, M. P. and A. Fornito (2014). "Brain Networks in Schizophrenia." Neuropsychology Review **24**(1): 32-48.

Vaskinn, A., K. Sundet, S. Friis, T. Ueland, C. Simonsen, A. B. Birkenaes, J. A. Engh, S. Opjordsmoen and O. A. Andreassen (2008). "Can learning potential in schizophrenia be assessed with the standard CVLT-II? An exploratory study." Scandinavian Journal of Psychology **49**(2): 179-186.

Veltman, D. J., S. A. R. B. Rombouts and R. J. Dolan (2003). "Maintenance versus manipulation in verbal working memory revisited: an fMRI study." NeuroImage **18**(2): 247-256.

Vernooij, M. W., M. Smits, P. A. Wielopolski, G. C. Houston, G. P. Krestin and A. van der Lugt (2007). "Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: A combined fMRI and DTI study." NeuroImage **35**(3): 1064-1076.

Vestergaard, M., K. S. Madsen, W. F. Baaré, A. Skimminge, L. R. Ejersbo, T. Z. Ramsøy, C. Gerlach, P. Åkeson, O. B. Paulson and T. L. Jernigan (2011). "White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children." Journal of Cognitive Neuroscience **23**(9): 2135-2146.

Voineskos, A. N., N. J. Lobaugh, S. Bouix, T. K. Rajji, D. Miranda, J. L. Kennedy, B. H. Mulsant, B. G. Pollock and M. E. Shenton (2010). "Diffusion tensor tractography findings in schizophrenia across the adult lifespan." Brain **133**(5): 1494-1504.

Wager, T. D. and E. E. Smith (2003). "Neuroimaging studies of working memory." Cognitive, Affective, & Behavioral Neuroscience **3**(4): 255-274.

Wagner, A. D., A. Maril, R. A. Bjork and D. L. Schacter (2001). "Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex." Neuroimage **14**(6): 1337-1347.

Wakana, S., A. Caprihan, M. M. Panzenboeck, J. H. Fallon, M. Perry, R. L. Gollub, K. Hua, J. Zhang, H. Jiang and P. Dubey (2007). "Reproducibility of quantitative tractography methods applied to cerebral white matter." Neuroimage **36**(3): 630-644.

Walter, H., A. P. Wunderlich, M. Blankenhorn, S. Schäfer, R. Tomczak, M. Spitzer and G. Grön (2003). "No hypofrontality, but absence of prefrontal lateralization comparing verbal and spatial working memory in schizophrenia." Schizophrenia Research **61**(2–3): 175-184.

Wassermann, D., N. Makris, Y. Rathi, M. Shenton, R. Kikinis, M. Kubicki and C.-F. Westin (2016). "The white matter query language: a novel approach for describing human white matter anatomy." Brain Structure and Function **221**(9): 4705-4721.

Waters, F. A. V., Johanna C. Badcock, Milan Dragovic, Assen Jablensky (2009). "Neuropsychological functioning in schizophrenia patients with first-rank (passivity) symptoms." Psychopathology **42**(1): 47-58.

Weiss, A. and S. Heckers (2001). "Neuroimaging of declarative memory in schizophrenia." Scandinavian Journal of Psychology **42**(3): 239-250.

Weiss, A. P., D. Goff, D. L. Schacter, T. Ditman, O. Freudenreich, D. Henderson and S. Heckers (2006). "Fronto-Hippocampal Function During Temporal Context Monitoring in Schizophrenia." Biological Psychiatry **60**(11): 1268-1277.

Weiss, A. P., D. L. Schacter, D. C. Goff, S. L. Rauch, N. M. Alpert, A. J. Fischman and S. Heckers (2003). "Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia." Biological psychiatry **53**(1): 48-55.

Weiss, A. P., M. Zalesak, I. DeWitt, D. Goff, L. Kunkel and S. Heckers (2004). "Impaired hippocampal function during the detection of novel words in schizophrenia." Biological psychiatry **55**(7): 668-675.

Weiss, E. M., C. Siedentopf, S. Golaszewski, F. M. Mottaghy, A. Hofer, C. Kremser, S. Felber and W. W. Fleischhacker (2007). "Brain activation patterns during a selective attention test — a functional MRI study in healthy volunteers and unmedicated patients during an acute episode of schizophrenia." Psychiatry Research: Neuroimaging **154**(1): 31-40.

Wheeler, A. L., M. M. Chakravarty, J. P. Lerch, J. Pipitone, Z. J. Daskalakis, T. K. Rajji, B. H. Mulsant and A. N. Voineskos (2014). "Disrupted prefrontal interhemispheric structural coupling in schizophrenia related to working memory performance." Schizophrenia bulletin **40**(4): 914-924.

Wheeler, A. L. and A. N. Voineskos (2014). "A review of structural neuroimaging in schizophrenia: from connectivity to connectomics." Frontiers in Human Neuroscience **8**(653).

Whitford, T. J., S. M. Grieve, T. F. Farrow, L. Gomes, J. Brennan, A. W. Harris, E. Gordon and L. M. Williams (2006). "Progressive grey matter atrophy over the first 2–3 years of illness in first-episode schizophrenia: a tensor-based morphometry study." Neuroimage **32**(2): 511-519.

Wilk, C. M., J. M. Gold, R. P. McMahon, K. Humber, V. N. Iannone and R. W. Buchanan (2005). "No, it is not possible to be schizophrenic yet neuropsychologically normal." Neuropsychology **19**(6): 778.

William M. Perlstein, P. D., Cameron S. Carter, M.D., Douglas C. Noll, Ph.D., and Jonathan D. Cohen, M.D., Ph.D. (2001). "Relation of Prefrontal Cortex Dysfunction to Working Memory and Symptoms in Schizophrenia." **158**(7): 1105-1113.

Wolf, D. H., R. C. Gur, J. N. Valdez, J. Loughead, M. A. Elliott, R. E. Gur and J. D. Ragland (2007). "Alterations of fronto-temporal connectivity during word encoding in schizophrenia." Psychiatry research **154**(3): 221-232.

Woods, S. W. (2003). "Chlorpromazine equivalent doses for the newer atypical antipsychotics." The Journal of clinical psychiatry.

Woolrich, M. W., S. Jbabdi, B. Patenaude, M. Chappell, S. Makni, T. Behrens, C. Beckmann, M. Jenkinson and S. M. Smith (2009). "Bayesian analysis of neuroimaging data in FSL." NeuroImage **45**(1, Supplement 1): S173-S186.

World Health Organization. (2017). "Schizophrenia."

Wu, X., X. Chen, Z. Li, S. Han and D. Zhang (2007). "Binding of verbal and spatial information in human working memory involves large-scale neural synchronization at theta frequency." Neuroimage **35**(4): 1654-1662.

Xiao, Y., S. Lui, W. Deng, L. Yao, W. Zhang, S. Li, M. Wu, T. Xie, Y. He, X. Huang, J. Hu, F. Bi, T. Li and Q. Gong (2015). "Altered Cortical Thickness Related to Clinical Severity But Not the Untreated Disease Duration in Schizophrenia." Schizophrenia Bulletin **41**(1): 201-210.

Zhang, R., M. Picchioni, P. Allen and T. Toulopoulou (2016). "Working Memory in Unaffected Relatives of Patients With Schizophrenia: A Meta-Analysis of Functional Magnetic Resonance Imaging Studies." Schizophrenia Bulletin **42**(4): 1068-1077.

Zhao, Y. L., S. P. Tan, F. D. Yang, L. L. Wang, W. F. Feng, R. C. K. Chan, X. Gao, D. F. Zhou, B. B. Li, C. S. Song, F. M. Fan, Y. L. Tan, J. G. Zhang, Y. H. Wang and Y. Z. Zou (2011). "Dysfunction in different phases of working memory in schizophrenia: Evidence from ERP recordings." Schizophrenia Research **133**(1): 112-119.

Zhou, D., C. Lebel, A. Evans and C. Beaulieu (2013). "Cortical thickness asymmetry from childhood to older adulthood." NeuroImage **83**: 66-74.

Zhou, Y., L. Fan, C. Qiu and T. Jiang (2015). "Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia." Neuroscience Bulletin **31**(2): 207-219.

Zijdenbos, A., R. Forghani and A. Evans (1998). Automatic quantification of MS lesions in 3D MRI brain data sets: Validation of INSECT. Medical Image Computing and Computer-Assisted Intervention — MICCAI'98: First International Conference Cambridge, MA, USA, October 11–13, 1998 Proceedings. W. M. Wells, A. Colchester and S. Delp. Berlin, Heidelberg, Springer Berlin Heidelberg**:** 439-448.

Zijdenbos AP, F. R., Evans AC. (2002). "Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis." Medical Imaging, IEEE Transactions on **21**(10): 1280-1291.

Supplementary Material

Supplementary Table I: *Left and Right FA Average Values (standard deviation) of all Fibre for both Groups*

	Controls		Patients	
	FA Left	**FA Right**	**FA Left**	**FA Right**
SLF	0.477 (0.004)	0.483 (0.004)	0.470 (0.004)	0.473 (0.005)
UF	0.433 (0.004)	0.447 (0.004)	0.424 (0.004)	0.436 (0.005)
SLF II	0.451 (0.006)	0.456 (0.006)	0.437 (0.006)	0.450 (0.008)
Arcuate	0.488 (0.006)	0.451 (0.032) [1]	0.496 (0.004)	0.474 (0.006)

[1] One control did not have an arcuate fasciculus, which is a finding documented in a number of study (Catani, Allin et al. 2007).

Supplementary Table II: *LI Average Values (standard deviation) of all Fibres for both Groups*

	Controls	Patients
SLF	-0.006 (0.004)	-0.002 (0.004)
UF	-0.005 (0.004)	-0.013 (0.004)
SLF II	-0.006 (0.007)	-0.014 (0.011)
Arcuate	0.075 (0.064)	0.023 (0.003)

Supplementary Table III: *Pearson Correlations Between the Cortical Thickness MFG Lateralization Values and the LI Values of the SLF and SLF II*

	Controls	Patients
	Cortical Thickness	**MGF Lateralization**
SLF LI	r=-0.50, p=0.06	r=0.07, p=0.81
SLF II LI	r=0.04, p=0.90	r=0.37, p=0.20

Supplementary Table IV: *Partial Pearson Correlations Between the Tasks and the LI Values of the SLF and SLF II, Controlled for Handedness*

	Controls		Patients	
	Passive Binding	**Active Binding**	**Passive Binding**	**Active Binding**
LI SLF	r=-0.39 p=0.17	r=-0.45 p=0.11	r=0.40 p=0.62	r=0.59 p=0.03
LI SLF II	r=-0,22 p=0.46	r=-0.13 p=0.67	r=0.03 p=0.91	r=0.51 p=0.08
Cortical Thickness LI	r=0.25 p=0.70	**r=0.66 p=0.01***	r=0.30 p=0.32	r=0.48 p=0.10

*Significant correlations, corrected FDR

Supplementary Table V: *Partial Pearson Correlations Between the Tasks and the LI Values of the SLF, and SLF II, Controlled for Handedness*

	Controls	Patients
	BaBp Contrast	**BaBp Contrast**
LI SLF	r=-0.31, p=0.28	**r=0.62, p=0.02***
LI SLF II	r=0.01, p=0.974	**r=0.63, p=0.02***
Cortical Thickness LI	**r=0.70, p=0.006***	r=0.46, p=0.12

*Significant correlations corrected FDR

Supplementary Table VI: *Pearson Correlations Anatomical Values and IQ for both Groups*

	Controls	Patients
	IQ	**IQ**
Ba	**r=0.59, p=0.02***	**r=0.61, p=0.02***
Bp	r=0.29, p=0.29	r=-0.36, p=0.21
BaBp	**r=0.62, p=0.01***	**r=0.61, p=0.02***

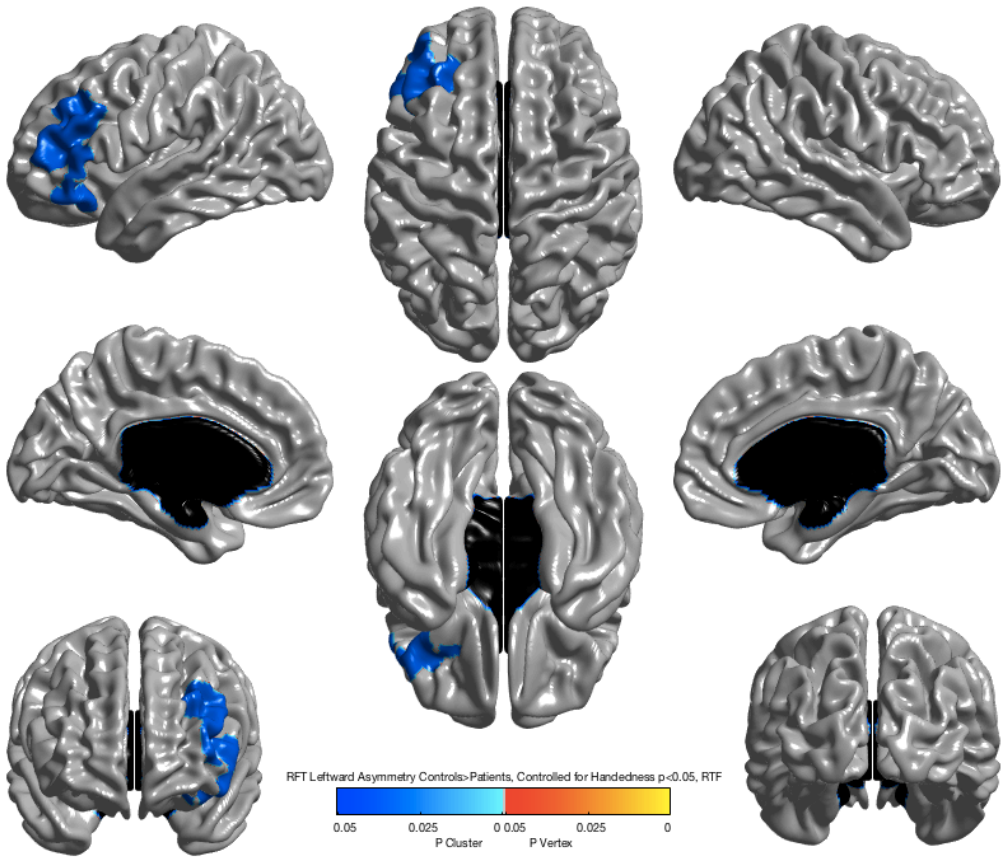
*Significant correlations corrected FDR

Supplementary Table VI: *Pearson Correlations Anatomical Values and Age for both Groups*

	Controls	Patients
	Age	**Age**
SLF FA Left	r=-0.22, p=0.44	r=-0.36, p=0.38
SLF FA Right	r=0.34, p=0.22	r=-0.27, p=0.36
SLF II FA Left	r=-0.31, p=0.28	r=-0.29, p=0.31
SLF II Right	r=0.00, p=1.00	r=0.23, p=0.43
LI SLF	**r=-0.69, p=0.004***	r=0.10, p=0.74
LI SLF II	r=-0.32, p=0.24	r=-0.40, p=0.16
Cortical Thickness LI	r=0.19, p=0.50	r=-0.54, p=0.05

*Significant correlations corrected FDR

Supplementary Figure 1*: Cortical Thickness Lateralization Group Differences, Corrected for Handedness*



Annex 1: Short paper that will be submitted to Schizophrenia Research shortly (Manuscript in Progress).

Petel Légaré, V. S. Grot, M. Néron, O.Lipp, D. Luck "The left superior longitudinal fasciculus contributes to active binding deficit in working memory in schizophrenia"

Title: The left superior longitudinal fasciculus contributes to active binding deficit in working memory in schizophrenia

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ABSTRACT

We investigated the contribution of the left superior longitudinal fasciculus (SLF) II integrity on active binding deficits in patients with schizophrenia (SZ). Fourteen patients and 15 matched controls performed a binding task, in which they were instructed to memorize actively or passively the combinations of three letters and three spatial locations. Tractography was used to estimate fractional anisotropy (FA) in the left SLF II. Patients with low-FA values exhibited a specific deficit of active binding, while patients with high-FA values performed equally well as controls. These results suggest that altered left frontal-parietal connectivity contributes to active binding dysfunction in SZ.

Keywords: working memory, memory binding, schizophrenia, tractography, superior longitudinal fasciculus

1. INTRODUCTION

In the past two decades, working memory (WM) deficits have emerged as a cardinal feature of schizophrenia (SZ). Researches revealed WM deficits across different tasks, stimuli modalities, or temporal components of events (see Park and Gooding, 2014 for a review). Recently, we shed light on an aspect of WM dysfunction that has received limited attention so far by examining the processing of multimodal stimuli, for which participants had to memorize the association between multiple information (Giersch et al., 2011; Grot et al., 2014, 2017; Luck et al., 2008, 2009, 2010). This associative process, usually referred to as binding, may be of great importance in SZ, as its disturbance might induce incomplete or inaccurate representations (Mitchell and Johnson, 2009). Using fMRI, we examined the neural correlates of two forms of binding using a task in which the participants had to memorize the combination of three words and three spatial locations (Grot et al., 2017). In the passive binding condition, letters and spatial locations were directly presented as bound. Conversely, in the active binding condition, words and spatial locations were presented as separated, and participants were instructed to intentionally create associations between them. Patients exhibited similar performance to the controls for passive binding, but significantly lower performance for active binding. FMRI analyses revealed that this active binding deficit was related to aberrant activity in the left frontal (superior and middle) and posterior parietal (inferior and superior) cortices during encoding. We interpreted these results as reflecting altered spatial attention in patients, that is required for correctly memorizing actively bound information in WM (Grot et al., 2017).

Frontal and parietal regions are connected through the superior longitudinal fasciculus (SLF), an associative fiber that has been frequently reported as altered in SZ (Canu et al. 2015; Pérez-Iglesias et al. 2010; Schaeffer et al., 2015; Shergill et al., 2007; Zeng et al., 2016). This white matter track is considered as composed of three different components: SLF I, II, and III (Makris

et al. 2005). Among them, the SLF II is of interest in this study as it connects posterior parietal and prefrontal cortices (Catani and de Schotten 2012; Wassermann et al. 2016). In addition, some evidence suggest that it contributes to WM processes in healthy individuals (Chechlacz et al., 2015; Kinoshita et al., 2016), but also in patients with SZ (Zeng et al., 2016). For instance, Zeng and collaborators (2016) reported a positive correlation between the left SLF integrity and WM performance.

The present study aimed to investigate whether active binding deficits reported in patients with SZ are related to the left SLF II integrity, using tractography. We hypothesized that: First, patients would exhibit altered white matter integrity in the SLF II relative to controls. Second, this alteration of white matter would be related to impaired active binding in patients.

2. MATERIAL AND METHODS

2.1. Participants

Fourteen outpatients and 15 healthy controls, group-matched for age, gender, handedness, parental socio-economic status, and IQ (Table S1), completed this study. All participants were part of a neuroimaging study being conducted at the Institut Universitaire en Santé Mentale de Montréal, Canada. Recruitment methods and inclusion/exclusion criteria have been previously reported (Grot et al., 2017). The Regroupement Neuroimagerie/Québec Ethical Review Board approved the study. All participants signed an informed consent form prior to the experiment and received financial compensation for their participation.

2.2. Measures

While in the scanner, participants performed a WM binding task (for more details see Grot et al., 2017). Briefly, they were instructed to memorize three words and three spatial locations they had to mentally bind (active binding) or that were directly presented as bound (passive binding).

For details about the diffusion-weighted images (DWI) acquisition and tractography processing, refer to Supplemental methods. Figure 1 illustrates trajectory of the left SLF II.

Figure 1 about here

2.3. Statistical analyses

Mean fractional anisotropy (FA) was used as a measure of white matter integrity (Beaulieu, 2002). A Student two-sample t-test was performed to measure group differences. In addition, correlation analyses were performed to explore the presence of potential confounds. Thus, the relationships between FA and age, education, and antipsychotic dose were examined. These factors were selected given their relationships with white matter integrity (Minami et al., 2003; Mori et al., 2007; Okugawa et al., 2004; Takase et al., 2004). B-Y method FDR corrections were applied to control for multiple comparisons (Narum, 2006).

Accuracy was estimated using the Pr index (Hits–False Alarms), to provide an objective measure of sensitivity that is independent of participant response bias (Snodgrass and Corwin, 1988). In order to establish if WM binding performance were related to SLF II integrity, we used a median split on FA values in both the SZ and control groups. We divided the two groups into a subgroup of high FA values (H-FA) and low-FA values (L-FA). Neither subgroups differed in sociodemographic, in clinical data, or in IQ ($p > 0.05$ in all cases). An analysis of variance (ANOVA) was performed with group (patients vs. controls) and FA level (H-FA vs. L-FA) as a

between-group factors, and binding conditions (active binding vs. passive binding) as a within-group factor. When needed, Duncan test comparisons were performed for post-hoc analyses.

The alpha level was set at 0.05 in all analyses.

3. RESULTS

3.1. Analyses of DTI data

The statistical analysis revealed that patient (mean: 0.44; SEM: 0.05) and control groups (mean: 0.45; SEM: 0.05) did not differ significantly on FA (t_{27}=1.60; p=0.12; d=0.39).

A set of correlations was also performed to examine the potential impact of sociodemographic characteristics, or medication on FA values. None of the analyses showed any significant correlations (all ps>0.05 after correction), indicating that SLF II integrity was unlikely influenced by these factors.

3.2. Impact of FA on behavioral performance

Pr scores are illustrated in Figure 2, and summarized in Table S2. The ANOVA showed a group X FA level X binding conditions significant interaction (F(1,25)=6.24; p=0.02; η^2=0.20). Post-hoc analyses revealed that the patients L-FA subgroup differed from the other three subgroups for active binding (all p< 0.004), but not for passive binding (all p> 0.5). No other comparison reached significance (all p> 0.24).

Figure 2 about here

4. DISCUSSION

Using tractography, we investigated the impact of frontal-parietal connectivity on WM binding in patients with SZ and healthy controls. More precisely, we examined whether the integrity of the SLF II contributed to the active binding deficit in patients we observed in a previous study (Grot et al., 2017). Contrary to our hypothesis, our analyzes showed that this tract was intact in patients with SZ. This result is in contradiction with previous studies which showed alterations of the SLF. However, there is no consensus as other studies failed to report such alterations (Guo et al., 2012; Zhou et al., 2017). In addition, only a few studies focused on the component II of the SLF specifically, not considering the temporal part of the whole SLF (Schaeffer et al., 2015). Another explanation relies on the limited sample of participants, although the computation of the effect size analysis showed that significant differences could be expected with a total sample size of 280 participants.

Our main result showed that the SLF II integrity was related to active binding performance in patients with SZ. Specifically, our analyzes revealed that patients with low FA values had a specific deficit of active binding, relative to patients with high FA values and controls, for whom binding performance did not appear to be influenced by FA values. As for patients with high FA values, no binding deficit was observed. Together, these results suggest that FA values may be an indicator for predicting active binding dysfunction, which we suggested as related to dysfunctions in attentional processes (see Grot et al., 2017 for an elaborated discussion).

Some limitations should be considered. Although our analyses revealed acceptable effect sizes, our samples remained modest. Thus, we consider that our results are preliminary and need to be evaluated within a larger cohort. In addition, the patients group exhibited intact IQ, which may have lead us to select high-functioning patients who may not be representative of the larger SZ population.

The present findings provide evidence to suggest that altered left frontal-parietal connectivity contributes to WM dysfunction in patients with SZ, and especially when they had to mentally create links between verbal and spatial information.

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Contributors

Author VPL performed tractography, analyzed the data, interpreted results, and wrote the first draft of the manuscript. Author SG acquired the data, and collaborated in the writing of the final version of the manuscript. author MN. Author MN contributed to the assessment of inter-rater reliability. Author OL supervised clinical assessments. Author DL conceptualized the study, supervised the study, provided laboratory space and resources for data analyses. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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REFERENCES

Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system — a technical review. N.M.R. Biomed. 15, 435–455.

Catani, M., de Schotten, M.Y., 2012. Atlas of human brain connections, Oxford University Press

Canu, E., Agosta, F., Filippi, M., 2015. A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease. Schizophr. Res. 161(1), 19-28

Chechlacz, M., Gillebert, C.R., Vangkilde, S.A., Petersen, A., Humphreys, G.W., 2015. Structural Variability within Frontoparietal Networks and Individual Differences in Attentional Functions: An Approach Using the Theory of Visual Attention. J. Neurosci. 35(30), 10647-10658.

Giersch, A., van Assche, M., Huron, C., Luck, D., 2011. Visuo-perceptual organization and working memory in patients with schizophrenia. Neuropsychologia. 49(3), 435-443.

Grot, S., Potvin, S., Luck, D., 2014. Is there a binding deficit in working memory in patients with schizophrenia? A meta-analysis. Schizophr. Res. 158(1-3), 142-145.

Grot, S., Légaré, V.P., Lipp, O., Soulières, I., Dolcos, F., Luck, D., 2017 Abnormal prefrontal and parietal activity linked to deficient active binding in working memory in schizophrenia. Schizophr. Res.

Guo, W., Liu, F., Liu, Z., Gao, K., Xiao, C., Chen, H., Zhao, J., 2012. Right lateralized white matter abnormalities in first-episode, drug-naive paranoid schizophrenia. Neurosci. Lett. 531(1), 5-9.

Kinoshita, M., Nakajima, R., Shinohara, H., Miyashita, K., Tanaka, S., Okita, H., Nakada, M., Hayashi, Y., 2016. Chronic spatial working memory deficit associated with the superior longitudinal fasciculus: a study using voxel-based lesion-symptom mapping and intraoperative direct stimulation in right prefrontal glioma surgery. J. Neurosurg. 125(4), 1024-1032.

Luck, D., Buchy, L., Lepage, M., Danion, J.M., 2009. Examining the effects of two factors on working memory maintenance of bound information in schizophrenia. J. Int. Neuropsychol. Soc. 15(4), 597-605.

Luck, D., Danion, J.M., Marrer, C., Pham, B.T., Gounot, D., Foucher, J., 2010. Abnormal medial temporal activity for bound information during working memory maintenance in patients with schizophrenia. Hippocampus 20(8), 936-948.

Luck, D., Foucher, J.R., Offerlin-Meyer, I., Lepage, M., Danion, J.M., 2008. Assessment of single and bound features in a working memory task in schizophrenia. Schizophr. Res. 100(1-3), 153-160.

Makris, N., Kennedy, D.N., McInerney, S., Sorensen, A.G., Wang, R., Caviness, V.S., et al., 2005. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb. Cortex 15, 854-869.

Minami, T., Nobuhara, K., Okugawa, G., Takase, K., Yoshida, T., Sawada, S., et al., 2003. Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. Neuropsychobiology 47(3), 141-145.

Mitchell, K.J., Johnson, M.K., 2009. Source monitoring 15 years later: What have we learned from fMRI about the neural mechanisms of source memory? Psychol. Bull. 135(4), 638-677.

Mori, T., Ohnishi, T., Hashimoto, R., Nemoto, K., Moriguchi, Y., Noguchi, H., et al., 2007. Progressive changes of white matter integrity in schizophrenia revealed by diffusion tensor imaging. Psychiatry Res. 154(2), 133-145.

Narum, S.R., 2006. Beyond Bonferroni: less conservative analyses for conservation genet- ics. Conserv. Genet. 7, 783–787.

Okugawa, G., Nobuhara, K., Minami, T., Tamagaki, C., Takase, K., Sugimoto, T., et al., 2004. Subtle disruption of the middle cerebellar peduncles in patients with schizophrenia. Neuropsychobiology 50, 119-123.

Park, S., Gooding, D.C., 2014. Working Memory Impairment as an Endophenotypic Marker of a Schizophrenia Diathesis. Schizophr. Res. Cogn. 1(3), 127-136.

Pérez-Iglesias, R., Tordesillas-Gutiérrez, D., Barker, G.J., McGuire, P.K., Roiz-Santiañez, R., Mata, I., de Lucas, E.M., Quintana, F., Vazquez-Barquero, J.L., Crespo-Facorro, B., 2010. White matter defects in first episode psychosis patients: a voxelwise analysis of diffusion tensor imaging. Neuroimage 49(1), 199-204.

Schaeffer, D.J., Rodrigue, A.L., Burton, C.R., Pierce, J.E., Unsworth, N., Clementz, B.A., McDowell, J.E., 2015. White matter structural integrity differs between people with schizophrenia and healthy groups as a function of cognitive control. Schizophr. Res. 169(1-3), 62-8.

Shergill, S.S., Kanaan, R.A., Chitnis, X.A., O'Daly, O., Jones, D.K., Frangou, S., et al., 2007. A diffusion tensor imaging study of fasciculi in schizophrenia. Am. J. Psychiatry 164, 467-473.

Snodgrass, J.G., Corwin, J., 1988. Pragmatics of measuring recognition memory: applications to dementia and amnesia. J. Exp. Psychol. Gen. 117(1), 34–50.

Takase, K., Tamagaki, C., Okugawa, G., Nobuhara, K., Minami, T., Sugimoto, T., et al., 2004. Reduced white matter volume of the caudate nucleus in patients with schizophrenia. Neuropsychobiology 50, 296-300.

Wassermann, D., Makris, N., Rathi, Y., Shenton, M., Kikinis, R., Kubicki, M., Westin, C.F., 2016. The white matter query language: a novel approach for describing human white matter anatomy. Brain. Struct. Funct. 221(9), 4705-4721.

Zeng, B., Ardekani, B.A., Tang, Y., Zhang, T., Zhao, S., Cui, H., Fan, X., Zhuo, K., Li, C., Xu, Y., Goff, D.C., Wang, J., 2016. Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. Schizophr. Res. 172(1-3), 1-8.

Zhou, Y., Liu, J., Driesen, N., Womer, F., Chen, K., Wang, Y., Jiang, X., Zhou, Q., Bai, C., Wang, D., Tang, Y., Wang, F., 2017. White Matter Integrity in Genetic High-Risk Individuals and First-Episode Schizophrenia Patients: Similarities and Disassociations. Biomed. Res. Int. 2017, 3107845.

Figure 1: Representative illustration of the SLF II in a participant.

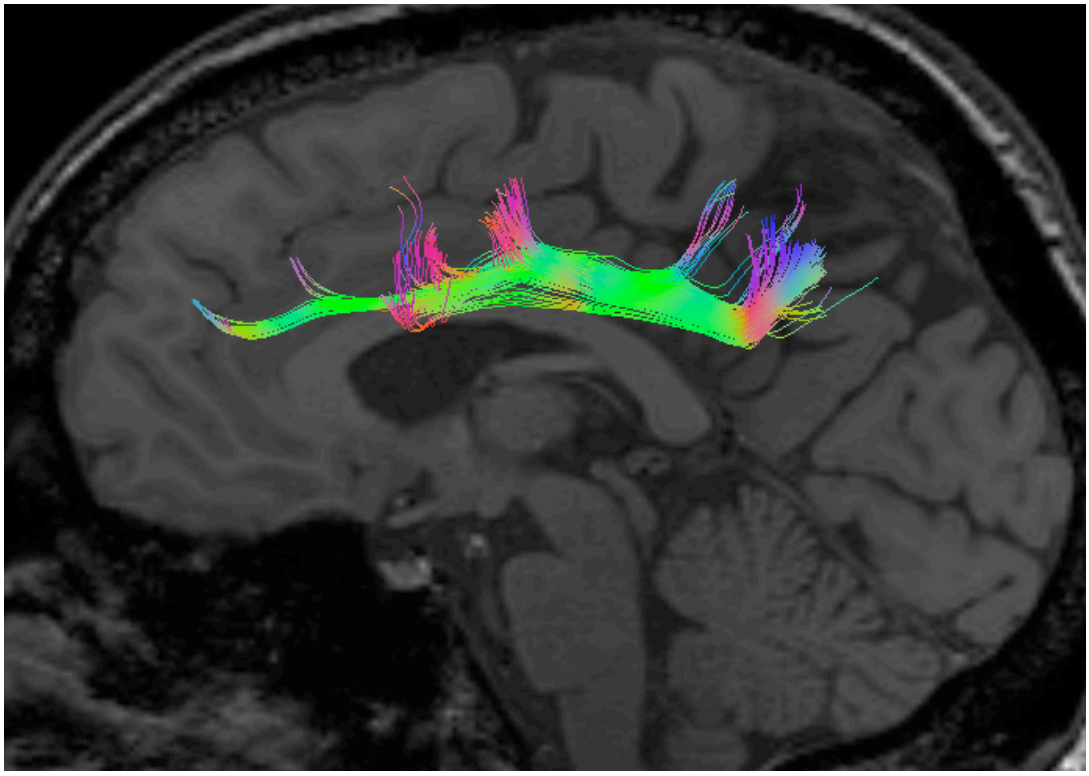

Figure 2: Behavioral performance. Mean Pr (hits – false alarms) scores for binding conditions are shown for patients and controls with low-FA values (L-FA) or high-FA values (H-FA). Errors bars represent SEM. * p< 0.004.