Brain Predictors of Negative Symptoms and Functional Outcomes in First-Episode Psychosis: A Multimodal Connectivity Approach

Marianne Khalil

Department of Psychiatry

McGill University, Montréal, Canada

April 2022

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master's in Science, Psychiatry Thesis

TABLE OF CONTENT

ABSTRACT

Psychosis strains individuals daily and can even impede their independence and productivity in society. Identifying predictors of functional outcomes at the first-episode psychosis (FEP) is crucial to tailor interventions with a rehabilitation and functioning improvement focus. Negative symptoms (NS), considered proxies for functional deficits, are hallmarks of psychosis associated with several neural substrates. Neuroimaging evidence, converging towards a dysconnectivity perspective of psychosis, has shown hub regions within brain networks to be disproportionally affected in schizophrenia, an effect correlated with symptoms of the disorder. The goal of this work is to examine brain markers of NS and functional outcomes in FEP, applying a connectivity approach that has been used chiefly for other symptoms. Leveraging both functional and structural imaging, betweenness centrality (BC) will assess the influence of hub regions on information processing in networks. In the first study, focusing on resting-state functional BC, we found a general increased abnormal hub influence of most whole-brain networks that correlated with functional deficits and NS. The right hippocampus was a significant predictor of overall functioning, an effect mediated by avolition/apathy. In the second study, leveraging qT1 structurally-derived BC for networks hubs and hippocampal subfields, we found reduced hub influence associated with functional deficits and NS. The left middle temporal gyrus, left CA4/DG, and right fornix were predictors of functional outcomes through avolition. We suggest that avolition is the underlying lack of drive that explains NS in psychosis requiring tailored interventions as a sensitive NS in FEP. Furthermore, leveraging BCs of two modalities, we propose that reduced hub centrality, or importance in connectivity, on a structural level in networks might impact how the brain remediates this loss by increasing the activity of other nodes to compensate. Finally, we discuss the potential creativity circuit between the middle temporal gyrus and the hippocampus underlying avolition and cognitive impairments in psychosis.

RÉSUMÉ

La psychose stresse les individus affectés quotidiennement et peut nuire à leur indépendance et productivité dans la société. Il est essentiel de déterminer les prédicteurs de l'issue fonctionnelle suite à un premier épisode de psychose (PEP) afin d'adapter les interventions axées sur l'amélioration du fonctionnement et la réadaptation. Les symptômes négatifs (SN), substituts pour les déficits fonctionnels, sont associés à plusieurs substrats neuronaux. Les données de la neuroimagerie, qui convergent vers une perspective de déconnexion de la psychose, suggèrent que les régions centrales des réseaux cérébraux, appelés « hubs », sont affectées de façon disproportionnée dans la psychose, et ce, en corrélation avec la gravité des symptômes. Le but du présent travail est d'examiner les marqueurs neuronaux des SN et les résultats fonctionnels suite à un PEP, en appliquant une approche de connectivité qui a été utilisée principalement pour d'autres symptômes psychotiques. En utilisant la centralité intermédiaire (CI) issue de l'imagerie fonctionnelle et structurelle, nous évaluerons l'influence des hubs sur le traitement de l'information dans les réseaux suite à un PEP. Dans la première étude, axée sur l'imagerie fonctionnelle au repos, nous avons constaté une augmentation généralisée de l'influence anormale de hubs dans la plupart des réseaux cérébraux. Cette augmentation était corrélée avec les déficits fonctionnels et les SN. L'hippocampe droit représentait un prédicteur important du fonctionnement global, un effet médié par l'avolition/apathie. Dans la deuxième étude, utilisant des marqueurs structurels pour la CI des hubs et des sous-champs hippocampiques, nous avons constaté que l'influence réduite des hubs était associée aux déficits fonctionnels et aux SN. Le gyrus temporel moyen, CA4/DG, et le fornix droit constituaient des prédicteurs de résultats fonctionnels médiés par l'avolition. Nous suggérons donc que l'avolition représente un manque de motivation sous-jacent qui explique les SN en psychose et nécessite des interventions adaptées en tant que SN sensible suite à un PEP. En tirant parti de deux modalités utilisant la CI nous avons aussi avancé

que la réduction de la centralité des hubs, ou de l'importance de la connectivité au niveau structurel dans les réseaux, pourrait avoir une incidence sur la façon dont le cerveau remédie à cette perte en augmentant l'activité d'autres hubs pour compenser. Enfin, nous discutons du circuit cérébral de la créativité, comprenant le gyrus temporel moyen et l'hippocampe. Un faible niveau de créativité pourrait expliquer l'avolition et les atteintes cognitives en psychose.

ACKNOWLEDGEMENTS

To start, this thesis would not have been possible without the participation of individuals from both the Montreal (QC) and London (ON) Prevention and Early Intervention for Psychosis Centers. Thank you to the participants, their families, and all the professionals in those two centers.

Throughout my master's I have received a great deal of support and assistance. My supervisor Dr. Martin Lepage has been a guiding figure and a listening ear for two years. Thank you for helping me in my search for clinical and imaging experience. My mentor throughout my studies Dr. Katie M. Lavigne was invaluable in helping me navigate the research world. Thank you for pushing me beyond my comfort zone and for accompanying me at every step.

I would also like to acknowledge the Canadian Institute for Health Research that funded my studies. The Canadian Graduate Scholarship allowed me to pursue my master's without any financial burden and with great pride from the beginning.

Thank you to my committee, Dr. Christine L. Tardif and Dr. Rachel Rabin. Your support and feedback were greatly appreciated over the two years.

Many thanks to Dr. Lena Palaniyappan and his lab for sharing their data with us and allowing me to work on it.

To my co-authors on my first published paper, Delphine and Philippine. Thank you for the discussions, the advice, and the laughs during this project. I will always cherish this paper.

To my blue room ladies, Agnès and Caroline. Thank you for embarking on this journey with me, listening to my ramblings, sharing your passions, and making this experience as human as possible during a pandemic. We had real crazy fun.

Thank you to Karyne for your constant energy at the lab and for taking care of us. You are what makes the lab a human hub!

Charlie, Gabby, and Gabriella thank you for your integration efforts. You were my first contact at the lab, and you eased me right into it! Vanessa, my work with you during my first year was unforgettable! It has been a pleasure learning alongside you while sharing memes.

To the CRISP research lab, it was an honor to work amongst you, exchanging and learning from each and every one of you. I had a great pleasure being your lab meeting coordinator for over a year and a half!

To all my friends who supported me throughout my master's. Thank you. You eased it on me and pushed me to the finish line.

Uncountable thanks to my family. An acknowledgment does not give you justice. You are the reason I am where I am today.

CONTRIBUTION OF AUTHOR

Marianne Khalil is the primary author of each chapter. She formulated the goals of the work, performed the analyses, interpreted, and discussed the results. The writing of this thesis is her own.

In the first study, the data was collected by multiple members of Dr. Martin Lepage's research lab as part of an ongoing longitudinal project started before Marianne's arrival. Nonetheless, she was trained for clinical work and was able to contribute to four participants in this study. She developed the processing pipeline for functional imaging and performed the quality control of all subjects included in the thesis.

In the second study, the data was collected by Dr. Lena Palaniyappan's research lab at Western University in London, Ontario. The raw clinical and processed imaging data were shared with Marianne for her to adapt and use in this work.

For the annex, Marianne is the first author of the meta-analysis. She developed and pre-registered the review protocol, performed the literature search, and brought together a group of students to work on this as collaborators. Philippine Hollander participated in the article's selection process. Katie M. Lavigne and Delphine Raucher-Chéné performed the quality control. The writing of the article, the analyses, and the development of the figures are her own.

CHAPTER 1: INTRODUCTION

Psychiatry has evolved to study, prevent, and treat mental disorders. The main goal of the field is to alleviate the burden of symptoms and daily shortcomings while trying to find interventions that can reverse the devastating impact of mental disorders (Martin, 2002). However, psychiatry has been seeking treatment without a prevention focus, a perspective that changed within the century. The integration of neuroscience and psychology research with psychiatry allowed for a multidimensional study of mental disorders in addition to successful prediction efforts observed in substance use disorders, dementia, and depression (Compton, 2008; Martin, 2002; Verdolini & Vieta, 2021). The search for markers of mental disorders for prevention has thus begun.

Rationale: Schizophrenia and related psychoses are debilitating psychiatric disorders affecting around 3% of the Canadian population (Public Health Agency of Canada, 2019) and are considered one of the top 20 most debilitating disorders worldwide (James et al., 2018). With a plethora of symptoms including delusions, emotional blunting, a lack of motivation, and cognitive deficits, it is one of the disorders that have attracted the most efforts to find preventive markers and treatments. It is a disorder with known at-risk and prodromal stages that have been studied and shown to improve outcomes with appropriate efforts (Compton, McGlashan, & McGorry, 2007). The study of schizophrenia symptoms recently shifted to include underlying neurological components that emphasize a connectivity perspective (Uddin, Yeo, & Spreng, 2019). Findings have highlighted interconnected symptoms and related brain deficits that informed the field on the etiology of the disorder and treatment avenues (Dong, Wang, Chang, Luo, & Yao, 2018).

Objectives: We aim to leverage the neurological dysconnectivity perspective to shed light on brain predictors of negative symptoms and functional outcomes in patients at early stages of psychosis. Our first study will use resting-state functional imaging while the second study will leverage structural imaging to build a connectivity profile using brain networks to focus on hub regions.

CHAPTER 2: LITERATURE REVIEW

1. Functional outcomes in schizophrenia: overview and importance

Schizophrenia (SZ) and related psychoses are characterized by positive (e.g., hallucinations, delusions), negative (e.g., reduced motivation and emotional expressivity), and cognitive (e.g., verbal memory impairments) symptoms (Kahn et al., 2015). Functional outcomes, defined as the ability to live independently, adapt to a community, and manage basic daily activities (American Psychiatric Association, 1987; Juckel et al., 2008; Sumiyoshi & Sumiyoshi, 2015), were included in 1987 as a diagnostic criterion in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1987) emphasizing their importance on the course of illness and treatment in psychosis (Juckel et al., 2008; Sumiyoshi & Sumiyoshi, 2015). Functioning deficits hold back SZ individuals impacting their ability to recognize a situation, take the appropriate decision, and perform a certain action (Harvey & Strassnig, 2012). A myriad of illness-related (e.g., cognitive impairments, negative symptoms), environmental (e.g., lack of social support, high unemployment rate), and demographic (e.g., immigration status, ethnicity) conditions worsen functioning of patients, restrict their control over daily activities, limit their financial independence, and isolate them from social integration and support (Harvey & Strassnig, 2012; Sumiyoshi & Sumiyoshi, 2015).

Functioning is assessed through a wide range of measures including employment, social functioning (i.e., level of interactions with others), and other comorbidities (e.g., depression) (Bromley & Brekke, 2010; Sumiyoshi & Sumiyoshi, 2015). The Global Assessment of Functioning (GAF) is an old functioning scale that subjectively and indistinguishably assesses social and occupational functioning in addition to clinical symptoms (Lehman, 1983; Samara et al., 2014). The scale is still widely used due to its overall capture of the current functioning of individuals (Suzuki, 2011). The Social and Occupational Functioning Assessment Scale (SOFAS)

is an improved version of the GAF and focuses on the individual's level of social and occupational functioning not directly influenced by overall symptoms (Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000; Samara et al., 2014). A longitudinal study by Samara et al. (2014) demonstrated that GAF and SOFAS scores are strongly and linearly correlated and can even be exchangeable.

Since there are no curative treatments for SZ yet, the main goals of interventions focus on reducing symptoms' interference with daily functioning and rehabilitating patients to function independently and productively in society (Bowie et al., 2008; Sumiyoshi & Sumiyoshi, 2015). Therapeutic efforts are focused on improving self-management by establishing routines to increase medication adherence, recognizing early signs of deterioration to decrease hospitalization rates, as well as surrounding individuals with supportive environments to improve social engagement and stabilize employment status (Shepherd et al., 2012). Overall, the aim is to alleviate the humanistic, social, and economic burdens that SZ puts on individuals, their families, and society (Bowie et al., 2008; De Silva, Hanwella, & De Silva, 2012; Millier et al., 2014). The psychosocial burden of SZ is significant as early as first-episode psychosis (FEP) and evidence suggest only slight functional deterioration with increased chronicity and severity of the disorder (Crespo-Facorro et al., 2021). Many efforts in early intervention services, specialized treatments targeting early stages of psychosis, have shown reduced symptoms and relapse risks, leading to improved long-term functional outcomes (Dama, Shah, et al., 2019; Falakshahi et al., 2020; Marder & Galderisi, 2017; Nolin, Malla, Tibbo, Norman, & Abdel-Baki, 2016; Norman et al., 2011) thus emphasizing the importance of identifying predictors of functioning at the FEP stage.

2. Clinical predictors of functional outcomes: a focus on negative symptoms

The study of functional outcomes has uncovered several predictors. Cognitive impairments, observed in the majority of individuals diagnosed with SZ, are present across a wide range of domains (i.e., attention, memory, executive functions, and social cognition) and have been

correlated with functional outcomes (Lepage, Bodnar, & Bowie, 2014). Specifically, verbal memory has been found to be a marker of functional outcomes as early as FEP (Lepage et al., 2014; Makowski et al., 2020). Demographically, age, gender, education, and race, have been shown to predict real-life daily functional capacity but not social capacity (Gould, Bowie, & Harvey, 2012). Sex differences studies have highlighted that men with SZ tend to be less educated, report more substance use disorders, and have longer premorbid adolescent stages which associate with poorer overall functioning (Dama, Veru, et al., 2019). In FEP, females had better functional outcomes in a longitudinal study, an effect associated with better verbal memory performance (Buck et al., 2020). Negative symptoms (NS) refer to the absence of normal behavior in SZ including social withdrawal, an inability to express emotions (e.g., pleasure), a lack of interest in the world, and an inability to act spontaneously (Ahmed et al., 2022; Blanchard & Cohen, 2006). These symptoms have been strongly correlated to functional outcomes, and with memory and social cognition, they account for most deficits observed in individuals' daily lives (Ang, Rekhi, & Lee, 2019; Vesterager et al., 2012). We will focus in this work on NS as proxies for functioning.

In SZ, NS are heterogeneous, appear as early as FEP, are resistant to treatment, and directly impact the functional outcomes of individuals (Lutgens et al., 2019; Strauss et al., 2018). The current literature proposes two different models of NS supported by longitudinal and correlational studies (Kirkpatrick, Fenton, Carpenter, & Marder, 2006; Millan, Fone, Steckler, & Horan, 2014). On one hand, a five-factor model separates NS into blunted affect (reduced emotional expression), alogia (poverty of speech), anhedonia (deficit in anticipating pleasure), asociality (diminished motivation to social interactions), and avolition (reduced motivation for goal-directed behavior) (Ahmed et al., 2022; Galderisi et al., 2021; Marder & Galderisi, 2017). On the other hand, a two-factor model clusters NS into two general domains: emotional expression (EXP: blunted affect and alogia) and motivation and pleasure (MAP: anhedonia, asociality, and avolition; Ang et al., 2019;

Galderisi et al., 2021). There is no consensus in the field as to which model is best suited to investigate NS in SZ individuals (Galderisi et al., 2021). However, a recent study by Ahmed et al. (2022) shows evidence of the five-factors model being more precise in uncovering associations compared to the two-factors model. In a study by Ang et al. (2019) leveraging both NS models, asociality, avolition, and MAP were correlated with overall functional deficits in SZ. In FEP, avolition, anhedonia, and passive/apathetic social withdrawal were found to correlate with poorer functional outcomes (Gutman et al., 2022; Van Erp et al., 2016). Although the different NS might overlap in their correlation with functional hallmarks of SZ, there is still no decisive convention on the optimal number of symptoms when investigating associations of NS with other dimensions of the disorder (Ahmed et al., 2022; Blanchard & Cohen, 2006).

3. Neurobiology of schizophrenia: an overview

Over the years, researchers in the field have tried to determine the underlying neurobiological correlates of SZ. The most common modalities used in SZ research have been structural and functional imaging which paint a complementary picture of the abnormal architecture and activity of the brain (Lynn & Bassett, 2019; Passingham, Stephan, & Kötter, 2002). In fact, there is a structural basis to functional brain activity although the association is not exclusive (Passingham et al., 2002; Rubinov & Sporns, 2010). High cost and insufficient clinically-relevant information have limited the use of other imaging modalities such as diffusion tensor imaging (structural), magnetoencephalography, functional near-infrared spectroscopy, and electroencephalography (functional; Sadeghi et al., 2021).

Structural imaging studies have consistently shown a widespread decrease in cortical gray matter volume in SZ, especially in frontal and medial temporal areas (Lepage et al., 2021; McHugo et al., 2020) as well as in subcortical structures including the hippocampus and amygdala (Gutman et al., 2022; Van Erp et al., 2016). Research focusing on surface area and cortical thickness, which

together constitute brain volume, has found extensive cortical thinning and reduced surface area across the cortical mantle in SZ (Van Erp et al., 2018). Severe grey matter volume reduction in brain regions such as the temporal lobe, fusiform gyrus, orbitofrontal cortex, and insula has shown significant correlations with increased NS severity in psychosis (Vieira et al., 2021). Even in FEP, neuroanatomical correlates of NS include larger ventricles (Akudjedu et al., 2020), reduced grey matter volume, and cortical thinning in the orbitofrontal and frontal inferior areas (Benoit, Bodnar, Malla, Joober, & Lepage, 2012; Kirschner et al., 2021). Apathy and avolition have been specifically associated with reduced frontal lobe volume in addition to cortical thinning in the orbitofrontal and anterior cingulate areas while blunted affect was associated with a larger surface area of the right putamen (Mørch-Johnsen, Agartz, & Jensen, 2017). Persistent NS, symptoms still present after 6 months of the FEP and directly related to poor functioning, have been associated with frontal and medial temporal abnormalities, especially a volume reduction of the hippocampus (Hovington & Lepage, 2012; Lavigne et al., 2022 (submitted); McHugo et al., 2020). The hippocampus, crucial for episodic memory, has been implicated in SZ functional deficits (Antoniades et al., 2018). Indeed, lack of EXP was predicted by a reduced hippocampal volume in FEP, an effect mediated by verbal memory impairments in a study by Duan et al. (2021).

Functional imaging studies of SZ have focused on a hypofrontality hypothesis, the observation that at rest, there is lower blood flow and activity in the anterior parts of the SZ brain (Friston, Brown, Siemerkus, & Stephan, 2016b; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011; Rubinov & Sporns, 2010), which is not consistently observed in FEP (González-Vivas et al., 2019). Studies with task-related functional imaging have shown abnormal activities in psychosis, either hypo- or hyper- activation, depending on the task and brain regions (González-Vivas et al., 2019; Niznikiewicz, Kubicki, & Shenton, 2003). The same generalized dysfunction is observed in FEP with reduced activation of the ventrolateral prefrontal cortex, the superior

temporal cortex, and the thalamus in attention tasks but increased activation in the ventrolateral prefrontal areas during working memory tasks (Schneider et al., 2007). In psychosis, NS have been associated with abnormal hypoactivity in the temporal lobe, altered activity in the inferior parietal lobule, hippocampus, and precuneus which worsen functional outcomes (Millan et al., 2014; Zhao et al., 2018). But, the impact of antipsychotic medication, heterogeneous structural and functional imaging findings, coupled with comorbid cognitive deficits and positive symptoms, have made it challenging to reach a consensus in terms of structural and functional regions with specific associations to NS and functioning (Millan et al., 2014).

4. Betweenness centrality: a new take on the neurobiology of schizophrenia

Beyond localized volume reductions or abnormal activation and deactivation throughout the cortex, connectivity is increasingly chosen to examine SZ. The focus shift comes with the dysconnectivity theory of psychosis which posits that psychotic symptoms are likely subtended by disruptions of integrated brain networks rather than damage in specific areas (Friston, Brown, Siemerkus, & Stephan, 2016a; Pettersson-Yeo et al., 2011; Rubinov & Sporns, 2010). Brain networks are representations of a complex system composed of nodes (i.e., brain regions) connected via edges (i.e., anatomical or functional connections) to each other (Rubinov & Sporns, 2010). Significant associations between nodes illustrate direct or indirect influences of one brain area on another and provide insight into disorder-related disruptions (Rubinov & Sporns, 2010). A meta-analysis performed by Khalil, Hollander, Raucher-Chéné, Lepage, and Lavigne (2022) from our team leveraged brain networks and provided new insights into the structural correlates of cognitive symptoms in SZ. Our meta-analysis confirmed that there is a structure for the function of the brain and that functionally-derived networks (i.e., Yeo et al. (2011)), when applied to structural findings, provided insights into cognitive deficits in SZ. We found that highly connected regions within networks correlated with specific domains and the number of networks associated

with a given domain were often indicative of the complexity of that domain (Khalil et al., 2022). The findings with cognitive symptoms, predictors of functional outcomes (see section 2), confirm the need to leverage a connectivity perspective while investigating NS as a proxy of functional outcomes in this thesis.

One well-known method to investigate brain networks is to first parcellate the brain leveraging Yeo et al. (2011) who identified 7 and 17 cortical brain networks from resting-state functional connectivity. These cortical networks were named based on their function as in the literature and include: the default mode network (DMN) active during rest as the default setting of the brain; the dorsal attention network (DAN) for externally directed attention to tasks; the frontoparietal control network (FPN) for goal-directed executive control; the limbic network (LIM) processing emotions and affect; the somatomotor network (SOM) responsible for movements and somatic sensations; the ventral attention network (VAN) for attention to salient stimuli and involuntary actions; and the visual network (VIS) groups regions of responsible for vision and direction in space.

Centrality, referring to the degree to which a given brain region (i.e., node) is densely connected to other brain structures has been used to investigate dysconnectivity in psychosis (Pettersson-Yeo et al., 2011; Rubinov & Bullmore, 2013; Rubinov & Sporns, 2010). Centrality focuses on hub regions, interconnected brain areas that play a crucial role in integrating neural signals, and includes multiple measures to assess the influence, shortest paths, and flow importance of hub nodes (Rubinov & Sporns, 2010). Hub regions have been shown to be disproportionately affected in SZ resulting in abnormal communication between brain regions and general dysconnectivity within and between brain networks, a hallmark of the disorder (Van den Heuvel et al., 2013). One measure of hub influence on a network is called betweenness centrality (BC) and refers to the influence of a given brain region (i.e., node) as it connects (via edges) to other brain structures. It is the fraction of all shortest paths in the network that pass through a given node

with a high BC symbolizing a hub region compared to other areas (Cheng et al., 2015; Rubinov & Sporns, 2010). Leveraging BC has delineated characteristics of psychosis (Van den Heuvel et al., 2013) and while connectivity, in general, has proven to be useful for cognitive symptoms (Khalil et al., 2022), there is a need to apply such approach to other dimensions of the psychopathology, notably NS. The heterogenous symptoms manifestations, myriad of functional impairments, and generalized structural and functional imaging abnormalities observed in SZ are best suited to be investigated with a BC measure to delineate the networks and subsequent hub regions underlying disorder-related deficits.

5. *Dysconnectivity underlying functional outcomes and negative symptoms*

As discussed previously, the field has moved to a dysconnectivity perspective with centrality measures (e.g., BC) better suited to investigate the complexity of SZ and its related clinical components as functional outcomes and NS. Functional imaging studies, with significant edges referring to simultaneous activation of nodes, have shown heterogeneous results. Reduced clustering and hub presence in medial parietal and premotor areas, right orbitofrontal areas, and reduced centrality in the superior temporal cortex were observed in some studies (Millan et al., 2014; Rubinov & Bullmore, 2013). Increased BC was observed in posterior hubs in a resting-state electroencephalogram study, another modality for functional connectivity (Krukow, Jonak, Karpiński, & Karakuła-Juchnowicz, 2019). Early-stage SZ showed high hub density in the FPN, VIS, and the right parahippocampus all associated with NS (Hummer et al., 2020; Zhou et al., 2022). Finally, the DMN had weaker connectivity between hubs such as the dorsal medial prefrontal cortex, the posterior cingulate cortex, and the precuneus in SZ individuals compared to controls but stronger connectivity between the temporal pole, medial motor cortex, and the anterior precuneus (Alonso-Solís et al., 2012). Overall, disrupted hubs activity with other brain areas is suggested to underlie NS, predictors of functional outcomes.

Although the usual method employed to derive centrality matrices uses resting-state functional magnetic resonance imaging (rs-fMRI) (Bullmore & Sporns, 2009), anatomically derived networks leveraging the Yeo et al. (2011) parcellation method have provided valuable insight (Khalil et al., 2022; Shafiei et al., 2020). In structural studies, with significant edges referring to more connections with other nodes, associations between the DMN and VIS were observed with cognitive deficits and NS, two stable hallmarks of SZ (Kirschner et al., 2020). Other morphometric studies showed a reduced BC in frontal areas in SZ and the emergence of non-frontal hubs compared to healthy controls (Bassett et al., 2008). A study by Makowski et al. (2020) from our group showed a reduced centrality of the hippocampus in FEP associated with NS, an effect mediated by poor verbal memory. By its position, the hippocampus and associated circuitry have been described as a convergence zone, connecting several cortical regions (Mišić, Goñi, Betzel, Sporns, & McIntosh, 2014). Previous models suggest cognitive deficits (e.g., verbal memory impairments) as precursors of NS which directly impact overall functioning (Foussias, Agid, Fervaha, & Remington, 2014). In Makowski et al. (2020), the decrease of cortical connections in the hippocampus was driven by output hubs mainly the subiculum, CA1, alveus, fimbria, and fornix. Structurally disrupted hubs in networks and subcortical regions might provide a window into NS and functional deficits in SZ.

To our knowledge, no study in the field has compared functional and structural BC as it relates to specific brain regions or networks in healthy or affected brains. The difference in interpretation of BCs between the modalities and the heterogeneity of disruptions to SZ brains add to the complexity of the comparison. However, studies in brain connectivity have shown that although there is a strong correlation between structural and functional connectivity, functional connectivity has also been observed with no subsequent correlations given than brain activity transcend local physical connections (Damoiseaux & Greicius, 2009). Thus, structural BC can be expected to

follow functional BC to a certain degree but the implications of heterogenous SZ brain disruptions remain unknown.

6. Rationale and objectives

SZ is a complex disorder with heterogenous NS manifestation, functional consequences, and underlying neural components. A better overall understanding of functional deficits with insights into predictors allows for personalized holistic treatments strategies established at the first signs of functional deficits, NS, or neuroimaging measures (Brissos, Molodynski, Dias, & Figueira, 2011). Nonetheless, previous studies have investigated predictors of functioning separately, usually with unidimensional measures of NS, or one modality for centrality. The heterogeneity of the disorder and the complex structure of its clinical and neural components is best suited to be investigated in a multidimensional fashion (Schultz et al., 2012). Leveraging structural and functional modalities provide a complementary understanding of the dysconnectivity theorized to be at the root of the disorder, in addition to the overlapping NS (Bullmore & Sporns, 2009; Cheng et al., 2015; Falakshahi et al., 2020).

The goal of this work is to determine brain markers of NS as proxies of functional outcomes in FEP, applying a connectivity approach coupled with multimodal imaging BC measures. We will first attempt to build a mediation model with functionally-derived BC, NS, and overall functioning, leveraging data collected during a large longitudinal study. We also want to highlight the NS that could potentially be markers in FEP. The size of the database used will provide us with an advantage compared to previous studies focusing on small samples. We will use this study to get an overall perspective of the association between functional deficits, NS, and BCs leveraging Yeo et al. (2011) networks and the hippocampus as one structure. In our second study, we will investigate structurally-derived BC, NS, and overall functioning at ultra-high-field neuroimaging. Previous studies on brain structure and NS have been limited in that they mainly employ MRI field

strengths (1.5T or 3T) that lack the spatial resolution to fully capture the complexity of networks and subcortical structures (De Martino et al., 2018). Using a different independent sample, we will have a higher precision focus on brain structures and the hippocampus to delimit hubs associated with NS that could predict functional deficits. To utilize the high resolution offered by the 7T scanner, we were prompted to use the structural images of this database as an independent sample from the first study. We expect NS to mediate the association between structural and functional BC and functional deficits. We hypothesize that large-scale and localized findings will be complementary although in two different modalities. Comparing the mediation models built in the two studies will provide insight into hub influence in FEP and predictors of functional outcomes.

CHAPTER 3: METHODS

1. Study 1: Resting-State Functional Connectivity in First-Episode Psychosis

1.1. Subjects

Subjects were recruited from the Prevention & Early Intervention Program for Psychoses (PEPP) at the Douglas Mental Health University Institute in Montreal, Canada, an early-intervention program integrated with clinical, teaching, and research services. The center caters to an area of ~300,000 people and specializes in individuals between 14 and 35 years old with a first episode of affective or non-affective psychosis (Iyer, Jordan, MacDonald, Joober, & Malla, 2015). Participants were enrolled as part of an ongoing longitudinal study, around Aripiprazole and cognitive improvement, which started in February 2016 (Lepage et al., 2021; Makowski et al., 2020; Raucher-Chéné et al., 2022). Included individuals (n = 100) followed the PEPP criteria which included an IQ > 70, a diagnosis of a nonaffective or affective psychosis, and a maximum of 1 month of antipsychotic medication history, reducing the potential confounding effects of long-term medication or prolonged illness course. Healthy controls (n = 60) were recruited through advertising in the same catchment area. Exclusion criteria included a personal or family history of a mental health or substance use disorder as defined by the American Psychiatric Association (2013). For both groups, individuals who were unable to undergo an MRI scan were excluded. In this chapter, we only included participants' data from the baseline time point, scanned before October 2021, and with a complete functional outcomes assessment. In total, our sample comprised of 49 controls and 41 FEP individuals tested within 3 months of entry at the PEPP. All participants provided written, informed consent and were free to withdraw from the study at any time with no consequences on treatment for FEP individuals.

1.2. Clinical variables: functional outcomes and negative symptoms

Functional outcomes of FEP were assessed with two scales. The SOFAS is a validated assessment focusing on the individual's level of functioning in everyday life not directly influenced by overall symptoms (Morosini et al., 2000). The SOFAS is scored on 100 with a total of 50 a serious impairment in overall functioning (Rybarczyk, 2011). The scale has high inter-rater reliability when raters have been trained or informed about scoring guidelines (Catts et al., 2011). The GAF scale (Lehman, 1983) was also used to assess functioning in this study and is rated from 0 to 100 with 100 being a superior functioning without impairments and 50 a serious to a severe deficit in everyday life (American Psychiatric Association, 1994). Although criticized for subjectively and indistinguishably assessing functioning in addition to clinical symptoms, studies have found GAF and SOFAS scores to be highly similar (Samara et al., 2014). Both strongly and negatively correlate with NS and have been shown to detect slight functional impairments even without symptoms manifestations (Samara et al., 2014).

NS were assessed for FEP participants with the Scale for Assessment of Negative Symptoms (SANS), a scale developed in conjunction with the Scale for Assessment of Positive Symptoms to provide an overall outlook on SZ (Andreasen, 1989). Although this is the first NS scale developed, its validity and inter-rater reliability haves been established over time independently of the NS model accuracy in the field (Kumari, Malik, Florival, Manalai, & Sonje, 2017). The scale measures 25 items grouped under five symptoms: affective blunting, alogia, avolition/apathy, anhedonia/asociality, and attention. Each element is rated on a scale of 0, absence of symptom, to 5, severe symptom intensity and presence (Andreasen et al., 2005; Galderisi et al., 2021). In accordance with the most recent guidelines, we excluded the attentional factor in addition to

recomputing the affective blunting and alogia domains' subtotals to respectively disregard items 6 (inappropriate affect) and 10 (poverty of content of speech; Galderisi et al., 2021).

1.3. Functional MRI acquisition

Subjects underwent a brain MRI scan on a 3T Siemens Magnetom Trio scanner at the Douglas Mental Health University Institute. Structural acquisition included a T1-weighted MPRAGE sequence (Brant-Zawadzki, Gillan, & Nitz, 1992): repetition time (TR) = 2,300 ms, echo time (TE) = 2.98 ms, field of view (FOV) = 256 mm, voxel size = 1 mm^3, 192 slices, flip angle = 9°, scan time ~ 5 min. Rs-fMRI acquisition used an echo-planar imaging BOLD sequence (Ogawa, Lee, Kay, & Tank, 1990) with TR = 928 ms, TE = 31 ms, FOV = 225 mm, voxel size = 2.5 mm^3, 52 slices, flip angle = 60°, scan time ~ 5 min. A scanner update performed on September 17th, 2018, changed the sequence TR from 928 to 951 ms. During the rs-fMRI, subjects were asked to close their eyes and rest without sleeping.

1.4. Functional preprocessing and quality control

We used the fmriPrep processing pipeline with the raw T1-weighted and rs-fMRI scans for a robust correction of acquisition artifacts and normalization of images. The homogenous T1-weighted structural images went through an intensity non-uniformity correction, where the skull is stripped and a template, the Montreal Neurological Institute 152 (MNI152), is applied to all images. The spatial normalization was followed by a brain tissue segmentation and then surfaces were reconstructed. In parallel, the functional images were pre-processed by overlapping a brain mask, estimating head motion, and correcting for slice-timing errors. After estimating the functional susceptibility to image distortions, the corrected T1-weighted images were aligned to the functional outputs. The fmriPrep pipeline resulted in a series of corrected structural and functional images standardized to an anatomical reference, the MNI152 (Esteban et al., 2019). Quality control

was done for both anatomical and functional images before and after fmriPrep, but none of the subjects had a final score lower than 1 on a 0-2 scale leading to the inclusion of all subjects.

1.5. Functional centrality: application of graph theory and betweenness centrality

Centrality was calculated with the CONN toolbox using BC, a measure of the degree of influence a specific region, or node, has on the overall network (Whitfield-Gabrieli & Nieto-Castanon, 2012). In MATLAB (MathWorks, 2021), using the CONN graphic user interface, the structural and functional outputs of fmriPrep were directly uploaded and we only ran functional smoothing as a local preprocessing step. Since the CONN toolbox needed TRs to compute graph theory measures, we processed the data before the scanner update and the data after the scanner update separately (see section 1.3). We selected the Yeo et al. (2011) networks as regions of interest (ROI) which do not include subcortical structures (i.e., amygdala, basal ganglia). Thus, we added the Automated Anatomical Labeling (AAL) atlas for specific parcellation of the hippocampus, a key region in psychosis. Denoising was not necessary in our case, therefore we directly performed a bivariate ROI-to-ROI non-weighted correlation as a first analysis followed by graph theory as a second analysis to calculate two-sided BC measures.

2. Study 2: Structural Connectivity in First-Episode Psychosis

2.1. Subjects

Data collection was conducted at Western University in Ontario, Canada. Subjects were recruited from the Prevention & Early Intervention Program for Psychoses at London Health Sciences Center, a community mental health program with a catchment area of ~390,000 people, that provides individuals in early psychosis between 14- and 30- years old with personalized treatment and support (London Health Sciences Centre, 2022). Participants were enrolled as part of a longitudinal observational study between February 2017 and March 2020 (Dempster et al., 2020;

Limongi, Jeon, Théberge, & Palaniyappan, 2021). Included patients (n = 62) were individuals with a FEP but medicated with antipsychotics for less than 14 days. They do not have the potential confounding effects of long-term medication or prolonged illness course. We only included data from the baseline time point and participants with complete NS and functioning assessments (n = 49). Non-clinical controls (n = 22) were recruited through posters advertising, matched for age, sex, and education level to patients, and had no mental illness history or family history (Dempster et al., 2020). Exclusion criteria included a substance use disorder, a history of major head injury, or contraindications for undergoing a scan (Dempster et al., 2020). All participants provided written informed consent including acceptance of subsequent use of their data.

2.2. Clinical variables: functional outcomes and negative symptoms

Functional outcomes of participants were assessed with SOFAS (Morosini et al., 2000). NS were assessed for all participants with the Brief Negative Symptoms Scale (BNSS, Strauss & Gold, 2016), a recent scale used to more finely assess six NS grouped into EXP (blunted affect and alogia) and MAP (anhedonia, distress, associability, and avolition; Ahmed et al., 2022; Galderisi et al., 2021; Kumari et al., 2017). Each symptom is rated from 0 to 6 based on severity, with scores of 2 or less considered a reduced presence of NS (Kirkpatrick et al., 2011; Mucci et al., 2019).

2.3. Structural MRI acquisition

Subjects underwent an MRI scan on a 7T Philips Achieva system with a 32-channel receive coil. Quantitative T1 (qT1) maps were acquired with a MP2RAGE sequence (Marques et al., 2010): TR = 6,000 ms, TE = 2.83 ms, first T1 = 800 ms, second T1 = 2,700 mm, first flip angle = 4°, second flip angle = 5°, FOV = 350 x 263 x 350 mm, scan time ~ 9 min 38 s. We employed qT1 mapping, a proxy for myelin content, to probe intracortical microstructure, which has been closely linked to connectivity and is more sensitive to symptoms in psychosis (Huntenburg et al., 2017;

Makowski et al., 2020; Makowski et al., 2019). The scans were then corrected for non-linear gradient fields using the Human Connectome Project pipelines (Glasser et al., 2013) followed by an automatized quality control prediction with the mriqc application (Esteban et al., 2017). A final MP2RAGE B1 correction was performed on sagittal slices as described in Eggenschwiler, Kober, Magill, Gruetter, and Marques (2012).

2.4. MRI processing and quality control

The uniform MP2RAGE images, similar to homogenous T1-weighted images (Marques et al., 2010), were submitted to the CIVET pipeline (Ad-Dab'bagh et al., 2006) to generate grey and white matter surfaces. The multiple automatically generated templated (MAGeT) algorithm was used to parcellate the hippocampus into nine sub-structures for each hemisphere (mammillary body, fornix, fimbria, CA1, subiculum, CA4/Dentate gyrus (DG), CA2/CA3, stratum radiatum/lacunosum/moleculare (SR/SL/SM), and alveus). Then, the CIVET-derived cortical surfaces and MAGeT-derived hippocampal subfields were used to sample the qT1 maps to obtain qT1 estimates for each vertex and hippocampal subfield as in Makowski et al. (2020). Quality control was done at each of the processing steps which led to the exclusion of four subjects for a final score lower than 1 on a 0-2 scale.

2.5. Structural centrality: application of graph theory and betweenness centrality

Centrality was calculated with the Brain Connectivity Toolbox (Rubinov & Sporns, 2010) using BC, a measure of the degree of influence a specific region, or node, has on the overall network. In MATLAB (MathWorks, 2021), vertex-based cortical qT1 estimates were parcellated into 62 brain regions using the Desikan Killiany-Tourville (DKT) atlas (Klein & Tourville, 2012). Subject-specific structural covariance matrices combining DKT-parcellated surfaces and hippocampal subfield volumes were calculated with jackknife bias estimation using group-level differences

converted to absolute values (Ajnakina et al., 2021; Das et al., 2018). Each of the 62 DKT brain regions (nodes) was categorized in the seven Yeo et al. (2011) networks (modules) with the hippocampus as its own module with eighteen nodes (left and right hemisphere estimates for each of the 9 subregions). BCs were then computed for each node, averaging over nodes to obtain a BC for each module. A high BC means that a specific node, for example, the left CA1/CA2 subfield, has more control over the module (e.g., the left hippocampus) due to more information passing through it. A lower BC would suggest that the node is not an important hub in the module compared to others (Cheng et al., 2015; Rubinov & Sporns, 2010).

3. Statistical Analyses

The two studies leveraged two different independent samples, NS assessment scales, and neuroimaging modalities to deduce BCs. However, we performed the same statistical analyses described below on the two samples.

3.1. Group differences

Using IBM SPSS software (IBMCorp, 2020), we performed a nonparametric Mann-Whitney U test to determine if there was a significant difference ($p < 0.05$) between demographic, clinical, and BC measures of FEP and controls. In the first study, the demographics compared included age, sex, years of education, and total IQ. In the second study, the demographics compared were age, sex, and years of education. In the first study, NS and functional outcomes were not assessed for controls while the second study allowed for group differences calculations for some clinical variables. Due to the violation of normality and homogeneity of variances observed in the samples, independent Student's t-tests were not possible (Mann & Whitney, 1947; Wilcoxon, 1945).

3.2. Correlation analyses

Then, we performed a partial correlation matrix controlling for age and sex, two variables shown to have significant effects on both imaging and clinical variables in psychosis (Buck et al., 2020; Makowski, Bodnar, Malla, Joober, & Lepage, 2016). We assessed the three-way association between each of the functionally-derived BCs, the NS, and functional outcomes in the first study and structurally-derived BCs, the NS, and functional outcomes in the second. Although our goal was to build mediation models, we first performed direct correlation analyses, controlling for age and sex to investigate if there are associations beyond what could be mediated. To control for multiple comparisons, we applied the False Discovery Rate (FDR), a robust control for loss of power in studies with high throughput, at the 0.05 level (Benjamini & Hochberg, 1995).

3.3. Mediation model

Significant correlations between NS and functional outcomes as well as NS and BCs were used to build mediation models between BCs, NS, and functional outcomes. We used the PROCESS v.3.5 macro developed by Andrew F. Hayes for SPSS to compute regression analyses for mediation analysis with age and sex as covariates (Hayes, 2012, 2017).

CHAPTER 4: RESULTS

1. Study 1: Resting-State Functional Connectivity in First-Episode Psychosis

1.1. Group differences

The demographic and clinical profiles of our sample are represented in Table 1. For group differences in BC measures, the results are illustrated in Figure 1. The DMN, FPN, SOM, and VIS networks show a significant difference in BCs between the FEP and control groups.

1.2. Functional outcomes and negative symptoms

Partial correlations, controlling for age and sex, revealed a significant and negative association between total SANS scores and SOFAS but not GAF. Figure 2 provides more details on the association between specific NS and functional outcomes. Avolition/apathy was the driver of NS-functional outcomes correlations.

1.3. Betweenness centrality: correlations with clinical variables

We performed a partial correlation matrix controlling for age and sex to determine associations between BCs and clinical variables in FEP. GAF was associated significantly and negatively with the SOM, DAN, VAN, FPN, LIM, and DMN networks. Similarly, SOFAS was significantly and negatively correlated with DAN, VAN, LIM, FPN, and DMN networks. After correcting for multiple comparisons with FDR at 0.05, the significant associations left were: GAF with the DAN, LIM, FPN, DMN, and VAN networks as well as SOFAS with the DAN network.

For NS, the SANS item avolition/apathy showed a significant positive correlation with BCs of the right hippocampus and the LIM network. See Figure 3 for the significant associations (before correction) between the three clinical variables. See Table S1 for all correlations computed. None of these associations survived FDR correction.

Table 1. Demographics for the two samples.

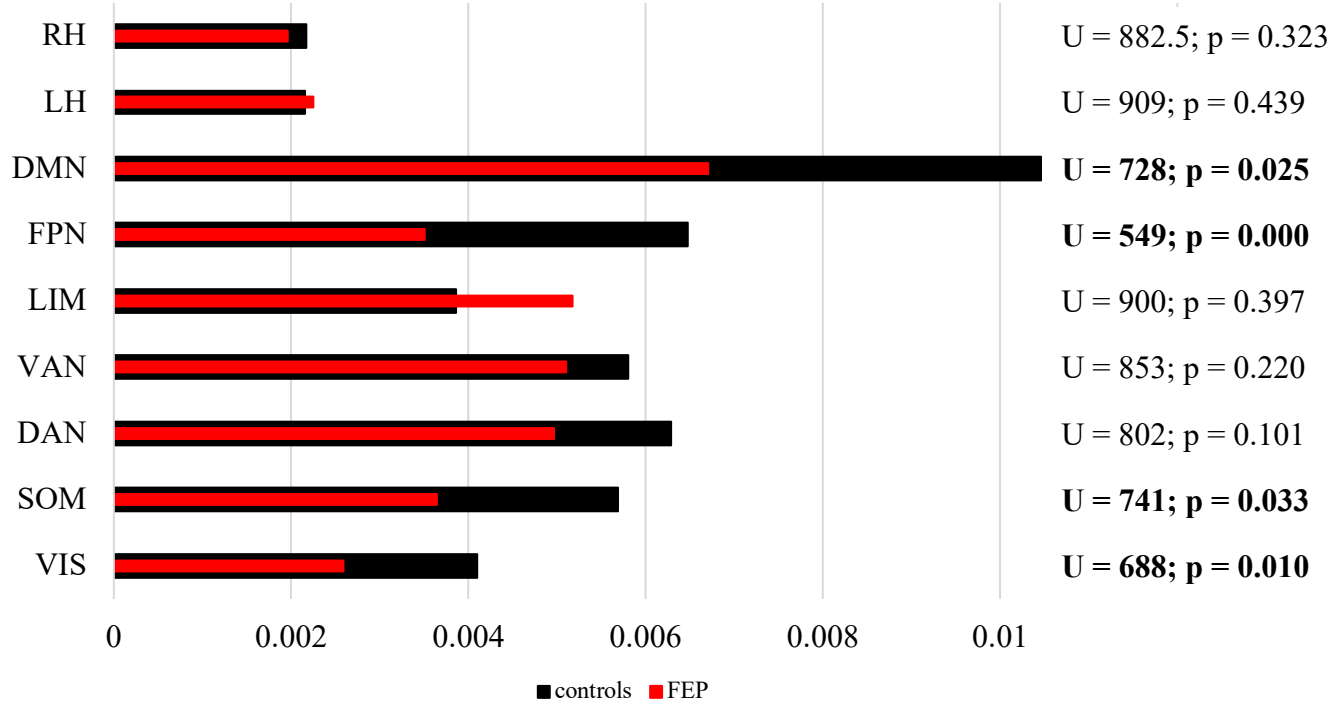
	Controls (n = 49)	**FEP (n = 41)**
Sex (males: females)	32:17	24:17
Age (y)	25.04 (4.50)	25.72 (4.29)
Handedness (right: left: ambidextrous)	49:0:0	36:2:3
Socioeconomic status (lower: middle: upper)	2:43:4	3:25:5[1]
Language (English: French: other)	29:12:8	23:12:5
Education (y)[a]	13.88 (1.58)	12.44 (2.21)
Full IQ[a]	108.55 (11.06)	102.71 (14.43)
Months since first episode at testing	-	1.86 (0.87)
CPZ at baseline	-	174.57 (123.18)[2]
Total SAPS	-	14.33 (14.59)[3]
Total PANSS-6	-	5.33 (4.73)[4]
Total SANS	-	7.54 (4.68)
Affective flattening/blunting	-	1.39 (1.43)
Alogia	-	0.66 (1.06)
Avolition/Apathy	-	2.20 (1.71)
Anhedonia/Asociality	-	2.17 (1.70)
SOFAS	-	55.78 (18.60)
GAF	-	51.05 (18.67)

Note: CPZ = chlorpromazine hydrocholoride equivalents; SAPS = Scale for the Assessment of Positive Symptoms; PANSS-6 = 6-items Positive and Negative Symptoms Scale; SANS = Scale for the Assessment of Negative Symptoms; SOFAS = Social and Occupational Functioning Assessment Scale; GAF = Global Assessment of Functioning. Values are presented as mean (standard deviation) if not indicated otherwise. Socioeconomic status was calculated in accordance with Hollingshead (1957).

[1]Missing data for 8 patients for socioeconomic status calculations.
[2]Missing data for 3 patients for CPZ.
[3]Missing data for 1 patient for SAPS.
[4]Missing date for 10 patients for total PANSS-6.

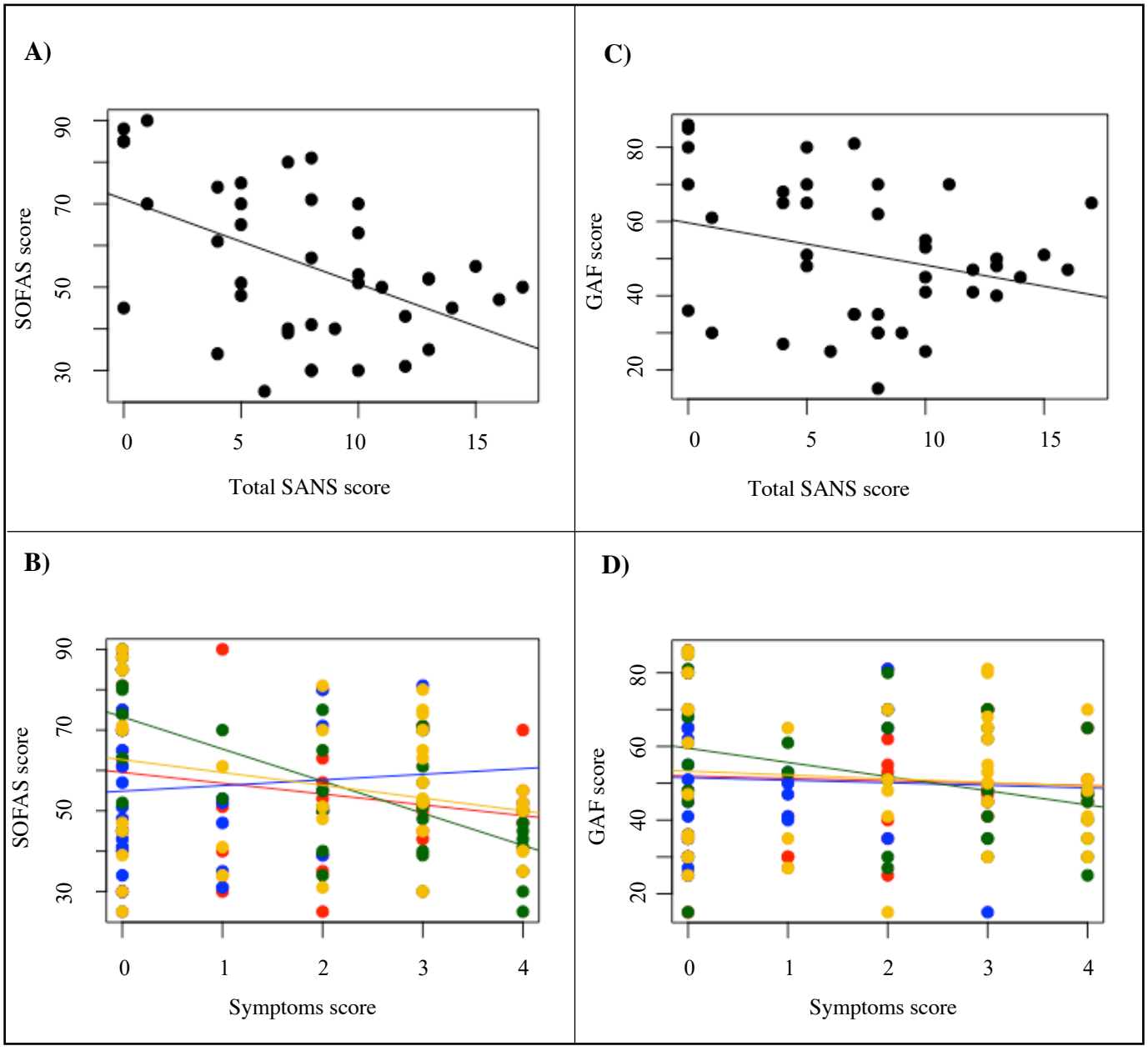
[a]Significant group difference ($p < 0.05$).

Figure 1. Comparison of mean BC measures between the two groups and results of the Mann-Whitney U test with p-value.



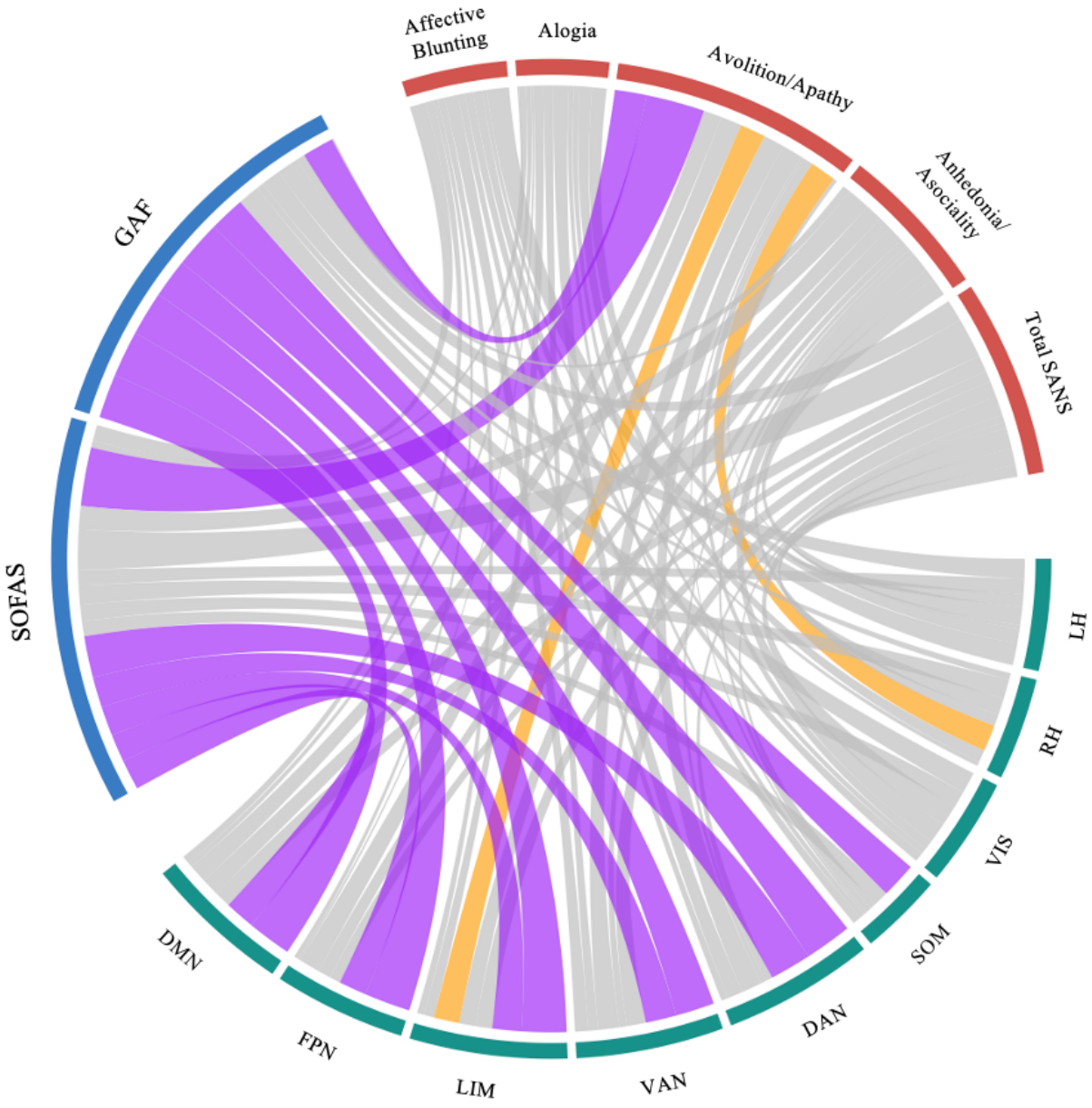
Note: RH = right hippocampus; LH = left hippocampus; DMN: default mode network; FPN = frontoparietal control network; LIM = limbic network; VAN = ventral attention network; DAN = dorsal attention network; SOM = somatomotor network; VIS = visual network. **Significant difference ($p < 0.05$).**

Figure 2. Scatterplot of the partial correlation controlling for age and sex between the SANS total and symptom scores and SOFAS and GAF scores of FEP participants.



Note: SOFAS = Social and Occupational Functioning Assessment Scale; SANS = Scale for Assessment of Negative Symptoms; GAF = Global Assessment of Functioning; red = affective blunting; blue = alogia; green = avolition/apathy; yellow = anhedonia/apathy.
A) Scatterplot of the partial correlation controlling for age and sex between the total SANS score and SOFAS score with $r = -0.511$, $p < 0.001$. B) Scatterplot of the partial correlation controlling for age and sex between affective blunting ($r = -0.206$, $p = 0.208$), alogia ($r = 0.086$, $p = 0.602$), avolition/apathy ($r = -0.748$, $p = 0.000$), anhedonia/apathy (-0.295, $p = 0.068$) and SOFAS scores. C) Scatterplot of the partial correlation controlling for age and sex between the total SANS score and GAF score with $r = -0.278$, $p > 0.05$. D) Scatterplot of the partial correlation controlling for age and sex between affective blunting ($r = 0.003$, $p = 0.986$), alogia ($r = 0.018$, $p = 0.914$), avolition/apathy (-0.406, $p = 0.010$), anhedonia/apathy (-0.103, $p = 0.534$) and GAF scores.

Figure 3. Circle plot of the correlations, controlling for age and sex, between functional outcomes, negative symptoms, and BC measures of FEP participants.

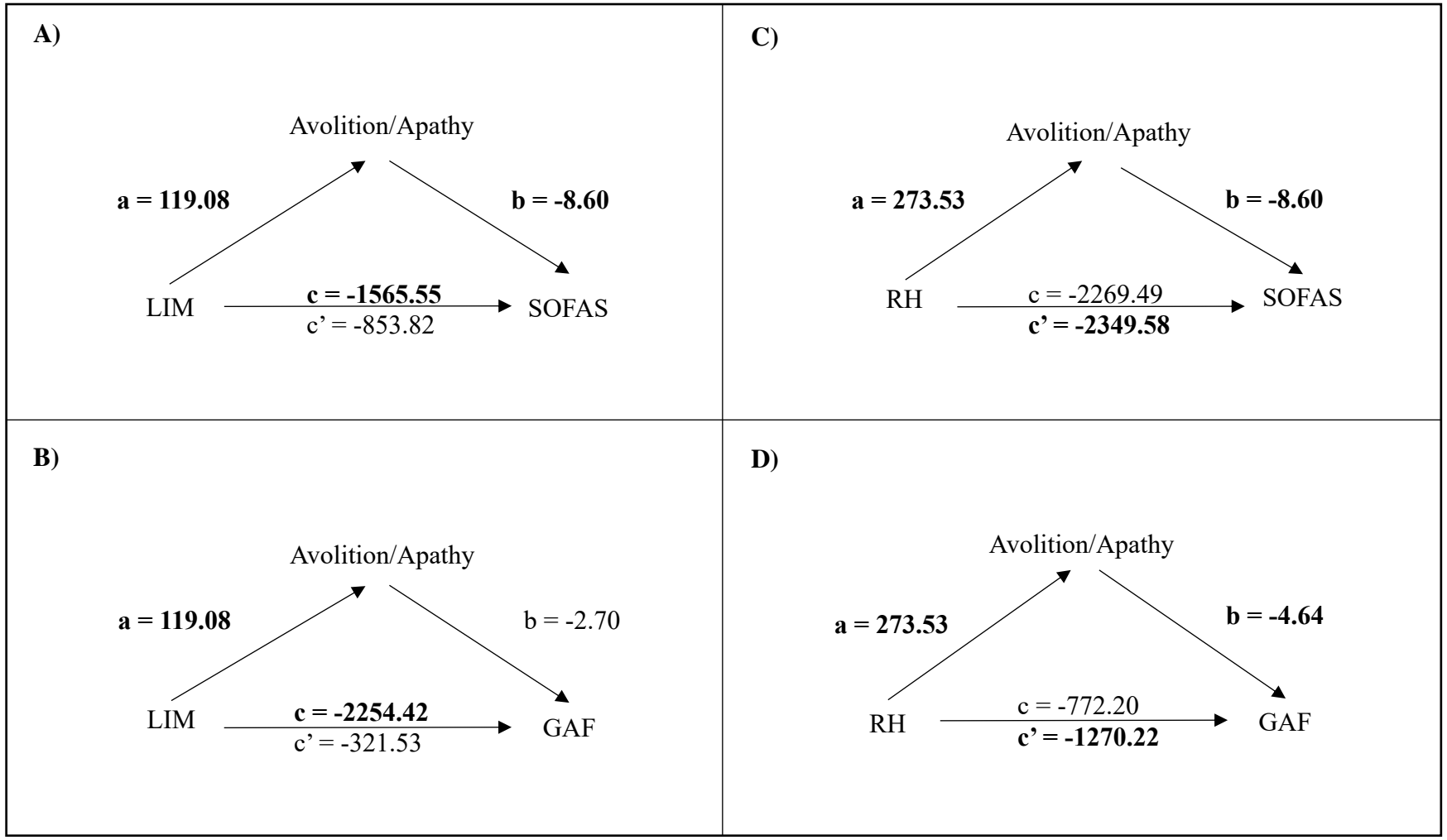


Note: SANS = Scale for Assessment of Negative Symptoms; LH = left hippocampus; RH = right hippocampus; VIS = visual network; SOM = somatomotor network; DAN = dorsal attentional network; VAN = ventral attentional network; LIM = limbic network; FPN = frontoparietal control network; DMN = default mode network; SOFAS = Social and Occupational Functioning Assessment Scale; GAF = Global Assessment of Functioning.
Associations illustrated are before correction for multiple comparisons. Grey links are non-significant associations. Purple links illustrate negative associations while orange links are for positive correlations. The width of links is proportional to the strength of the correlation

1.4. Mediation models

A pre-requisite of mediation models is a significant correlation between the mediator and the predictor as well as the mediator and the outcomes variable (Schoemann, Boulton, & Short, 2017). In this case, significant BCs-NS, and NS-overall functioning associations were required to determine if there is an indirect effect of BCs on functioning mediated by NS. Based on results from 1.3, there was a significant correlation between avolition/apathy with overall functioning. Resting-state functional connectivity highlighted the LIM network and the right hippocampus with BCs significantly associated with avolition/apathy. No other NS showed a significant direct correlation between a functional scale and a brain network. Therefore, we considered that avolition/apathy could be a proxy for our mediation model. The results of the mediation model controlling for age and sex are illustrated in Figure 4. Although the total effect of the right hippocampus BC on functional outcomes was not significant, the indirect effect through avolition/apathy was significant for both SOFAS and GAF.

Figure 4. Mediation model between the LIM and right hippocampus BCs, avolition/apathy, and SOFAS and GAF in FEP participants controlling for age and sex.



Note: LIM = limbic network; RH = right hippocampus; SOFAS = Social and Occupational Functioning Assessment Scale; GAF = Global Assessment of Functioning.

2. Study 2: Structural Connectivity in First-Episode Psychosis

2.1. Group differences

Demographics and performance scores for the groups are presented in Table 2. Results of structural BCs comparisons between the two samples are presented in Figure 5. Hubs with significant differences between controls and FEP are the left lateral orbitofrontal gyrus in the LIM network, the left calcarine part of the VIS network, the left isthmus of the cingulate gyrus associated with the DMN network, the right precentral gyrus, and the right postcentral gyrus, both in the SOM network. In the hippocampus, the left subiculum is the only subfield with a significant difference in BC measures between the two groups.

2.2. Functional outcomes and negative symptoms

The partial correlation matrix, controlling for age and sex, investigated the associations between NS and overall functioning. Results are illustrated in Figure 6. Avolition was the only element with a significant negative correlation with functional outcomes. Distress and associability showed near-significant associations with functional outcomes. The total scores for EXP and MAP showed no significant correlations.

Table 2. Demographics for the two samples.

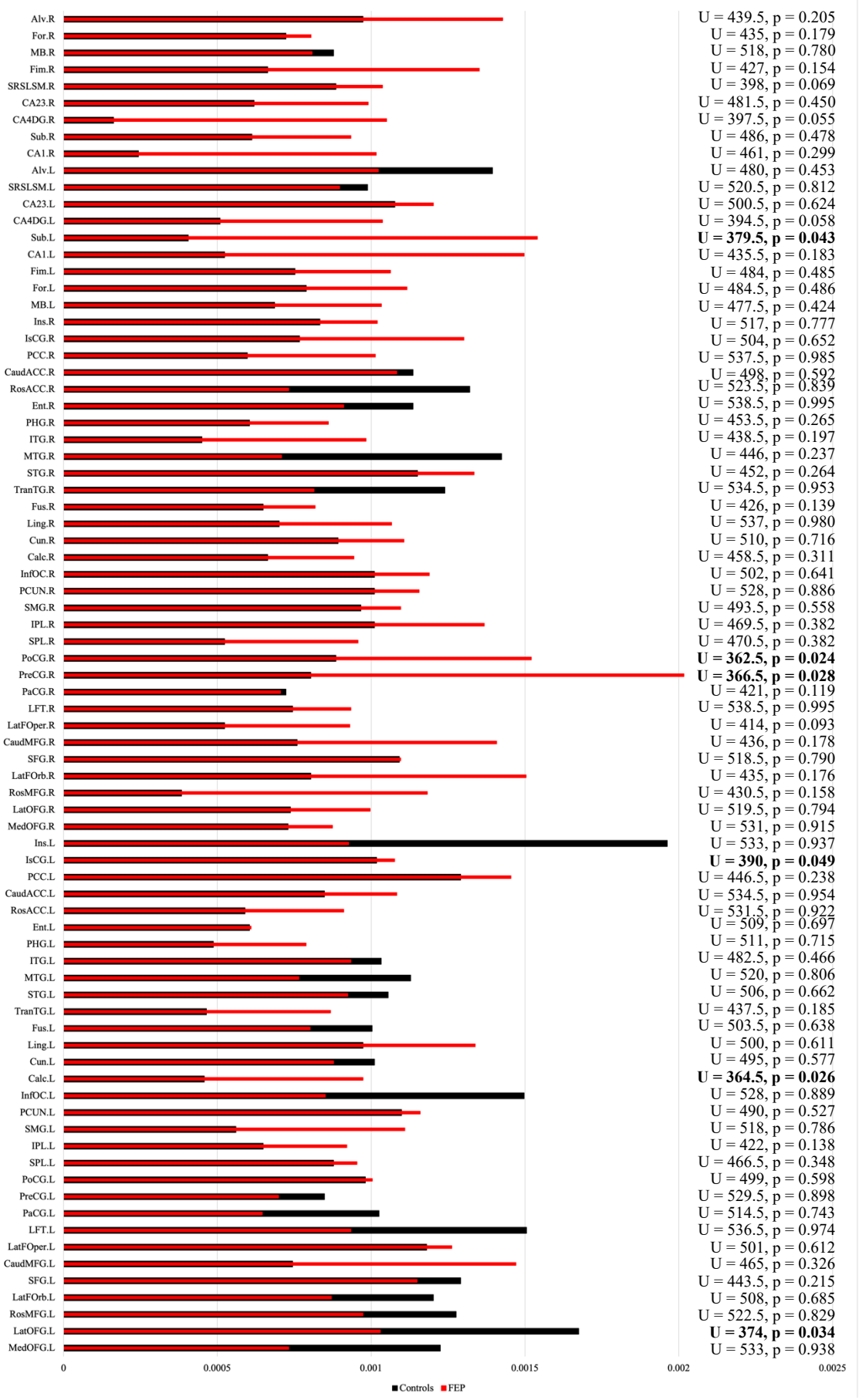
	Controls (n = 22)	**FEP (n = 49)**
Sex (males: females)	14:9	39:10
Age (y)	22.80 (4.21)	21.13 (3.40)
Socioeconomic status (lower: middle: upper)	7:12:3	10:32:1[1]
Education (y)	13.50 (1.92)	13.12 (1.89)
Months since first episode at testing	-	1.04 (1.89)[2]
PANSS-8 Positive Symptoms[a]	3.00 (0.00)	12.41 (2.59)
PANSS-8 Negative Symptoms[a]	3.00 (0.00)	7.16 (4.11)
Total BNSS	-	22.98 (18.02)
Anhedonia	-	7.12 (5.52)
Associability	-	3.43 (2.93)
Avolition	-	3.67 (3.19)
Distress	-	1.18 (1.38)
Blunted affect	-	4.90 (5.16)
Alogia	-	2.67 (3.60)
EXP	-	5.23 (7.57)
MAP	-	10.63 (11.71)
Total SOFAS[a]	82.77 (4.28)	40.43 (12.24)

Note: SAPS: Scale for the Assessment of Positive Symptoms; PANSS-8 = 8-items Positive and Negative Symptoms Scale; BNSS = Brief Negative Symptom Scale; EXP = emotional expressivity; MAP = motivation and pleasure; SOFAS = Social and Occupational Functioning Assessment Scale. Values are presented as mean (standard deviation) if not indicated otherwise.

[1]Missing data for 6 participants.
[2]Missing data for 13 participants.

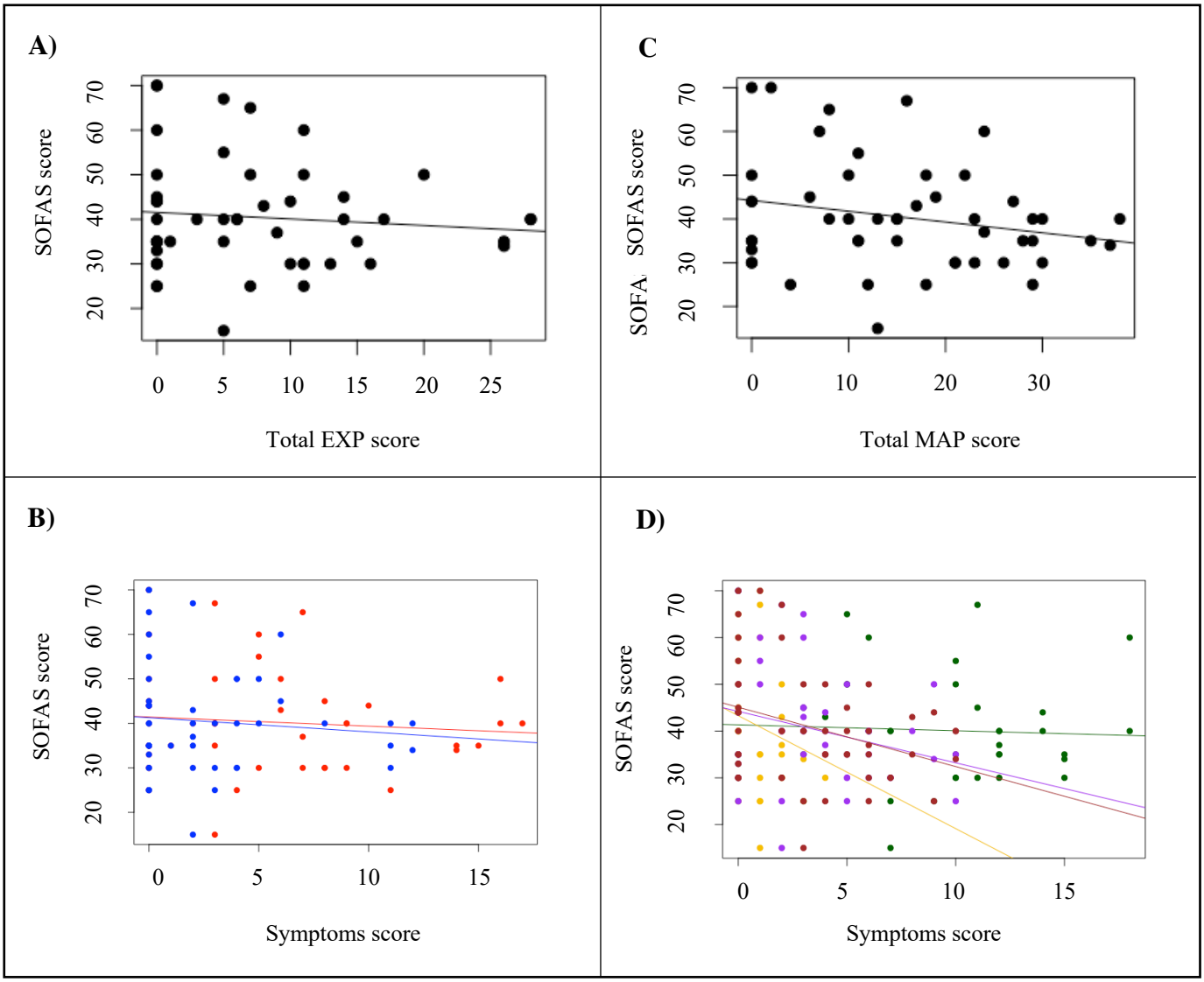
[a]Significant group difference ($p < 0.05$).

Figure 5. Comparison of mean BC measures between FEP participants and controls and results of the Mann-Whitney U test with p-value.



Note: In list order: right hippocampal alveus, right hippocampal fornix, right hippocampal mammillary bodies, right hippocampal fimbria, right hippocampal stratum radiatum, lacunosum, moleculare, right hippocampal CA2/CA3, right hippocampal CA4/dentate gyrus, right hippocampal subiculum, right hippocampal CA1, left hippocampal alveus, left hippocampal stratum radiatum, lacunosum, moleculare, left hippocampal CA2/CA3, left hippocampal CA4/dentate gyrus, left hippocampal CA1, left hippocampal fimbria, left hippocampal fornix, left hippocampal mammillary bodies, right insula (VAN), right isthmus cingulate gyrus (DMN), right posterior cingulate cortex (FPN), right caudal anterior cingulate cortex (VAN), right rostral anterior cingulate cortex (DMN), right entorhinal cortex (LIM), right parahippocampal gyrus (LIM), right inferior temporal gyrus (LIM), right middle temporal gyrus (DMN), right superior temporal gyrus (SOM), right transverse temporal gyrus (SOM), right fusiform gyrus (VIS), right lingual gyrus (VIS), right cuneus (VIS), right calcarine (VIS), right inferior occipital cortex (VIS), right precuneus (DMN), right supramarginal gyrus (FPN), right inferior parietal lobule (DMN), right superior parietal lobule (DAN), right postcentral gyrus (SOM), right precentral gyrus (SOM), right paracentral gyrus (SOM), right lateral frontal pars triangularis (FPN), right lateral frontal pars opercularis (FPN), right caudal middle frontal gyrus (FPN), right superior frontal gyrus (DMN), right lateral frontal pars orbitalis (DMN), right rostral middle frontal gyrus (FPN), right lateral orbitofrontal gyrus (LIM), right medial orbitofrontal gyrus (LIM), left insula (VAN), left isthmus cingulate gyrus (DMN), left posterior cingulate cortex (FPN), left caudal anterior cingulate cortex (VAN), left rostral anterior cingulate cortex (DMN), left entorhinal cortex (LIM), left parahippocampal gyrus (LIM), left inferior temporal gyrus (LIM), left middle temporal gyrus (DMN), left superior temporal gyrus (SOM), left transverse temporal gyrus (SOM), left fusiform gyrus (DAN), left lingual gyrus (VIS), left cuneus (VIS), left calcarine (VIS), left inferior occipital cortex (VIS), left precuneus (DMN), left supramarginal gyrus (VAN), left inferior parietal lobule (DMN), left superior parietal lobule (DAN), left postcentral gyrus (SOM), left precentral gyrus (SOM), left paracentral gyrus (SOM), left lateral frontal pars triangularis (DMN), left lateral frontal pars opercularis (DMN), left caudal middle frontal gyrus (DMN), left superior frontal gyrus (DMN), left lateral frontal pars orbitalis (DMN), left rostral middle frontal gyrus (FPN), left lateral orbitofrontal gyrus (LIM), left medial orbitofrontal gyrus (LIM). **Significant difference ($p < 0.05$).**

Figure 6. Scatterplot of the partial correlation controlling for age and sex between the domain and symptoms scores of BNSS and SOFAS in FEP participants.



Note: SOFAS = Social and Occupational Functioning Assessment Scale; EXP = emotional expressivity; MAP = motivation and pleasure; red =blunted affect; blue = alogia; green = anhedonia; yellow = distress; purple = associability; brown = avolition.

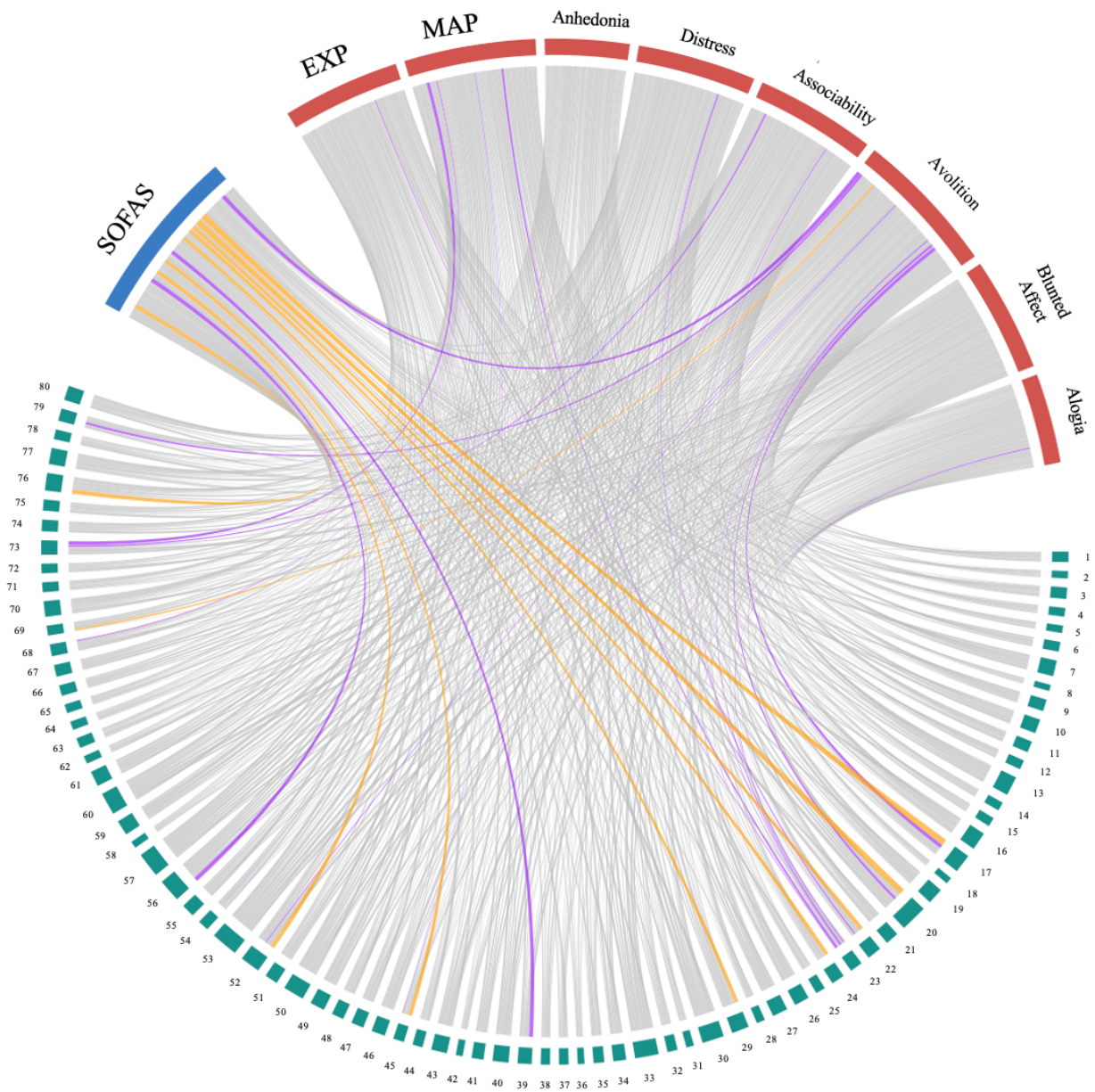
A) Scatterplot of the partial correlation controlling for age and sex between the total EXP score and SOFAS score with r = -0.096, p = 0.522. B) Scatterplot of the partial correlation controlling for age and sex between blunted affect (r = -0.085, p = 0.570), alogia (r = 0.092, p = 0.537) and SOFAS scores. C) Scatterplot of the partial correlation controlling for age and sex between the total MAP score and SOFAS score with r = -0.230, p = 0.119. D) Scatterplot of the partial correlation controlling for age and sex between anhedonia (-0.060, p = 0.689), distress (r = -0.273, p = 0.063), associability (r = -0.263, p = 0.074), avolition (r = -0.336, r = 0.021) and SOFAS scores.

2.3. Betweenness centrality: correlations with clinical variables

We performed partial correlations with age and sex as covariates to find correlations between BCs of brain hubs or hippocampal subfields, NS, and overall functioning (Figure 7 and Table S2). Functional outcomes were significantly and positively correlated with BCs of the left calcarine (VIS), the left fusiform (DAN), the left superior temporal gyrus (SOM), the left inferior temporal gyrus (LIM), the left posterior cingulate cortex (FPN), the right supramarginal gyrus (FPN), the right transversal temporal gyrus (VAN), and the right SR/SL/SM (hippocampus). Functioning was negatively associated with the right lateral frontal pars triangularis (FPN), and the right parahippocampal gyrus (LIM).

For NS, EXP from the BNSS showed a negative and significant correlation with the left middle temporal gyrus (DMN) driven by alogia. MAP was significantly and negatively correlated with the left middle temporal gyrus (DMN), the right supramarginal gyrus (FPN), the left CA4/DG (hippocampus), and the right subiculum (hippocampus). Avolition was significantly and negatively associated with the left calcarine (VIS), the left fusiform gyrus (DAN), the left middle temporal gyrus (DMN), the right transversal temporal gyrus (VAN), the left CA4/DG (hippocampus), the left CA2/3 (hippocampus) and the right fornix (hippocampus). Significant and negative correlations were observed between distress and the left superior temporal gyrus (SOM), anhedonia and the right middle temporal gyrus (DMN) and subiculum (hippocampus), as well as associability and the left middle temporal gyrus (DMN) and the right subiculum (hippocampus). None of the mentioned correlations survived FDR correction at 0.05.

Figure 7. Circle plot of the correlations, controlling for age and sex, between functioning, negative symptoms, and structural connectivity in FEP.



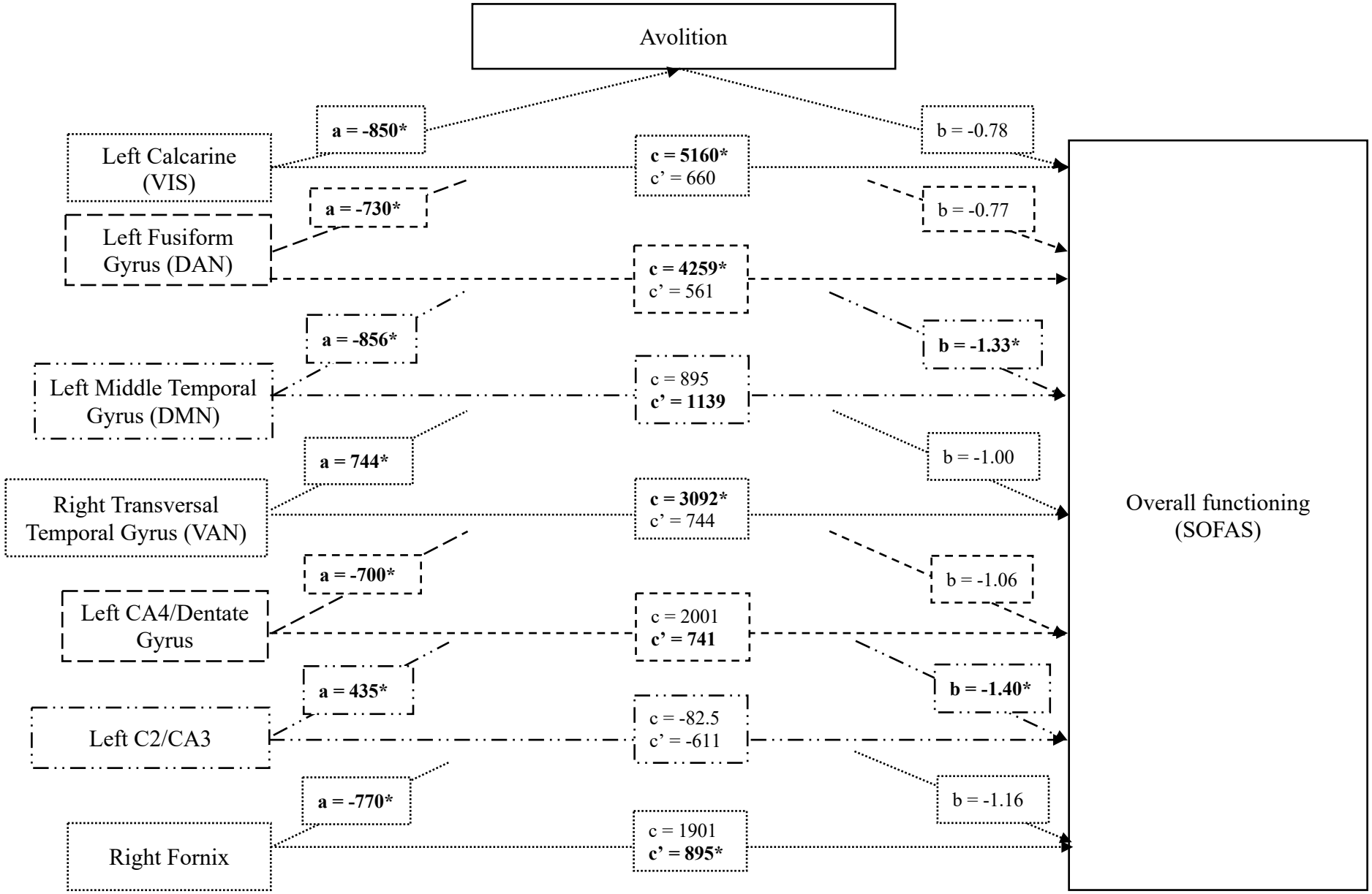
Note: SOFAS = Social and Occupational Functioning Scale; EXP = emotional expressivity; MAP = motivation and pleasure; 1= Left medial orbitofrontal gyrus (LIM); 2= Left lateral orbitofrontal gyrus (LIM); 3= Left rostral middle frontal gyrus (FPN); 4= Left lateral frontal pars orbitalis (DMN); 5= Left superior frontal gyrus (DMN); 6= Left caudal middle frontal gyrus (DMN); 7= Left lateral frontal pars opercularis (DMN); 8= Left lateral frontal pars triangularis (DMN); 9= Left paracentral gyrus (SOM); 10= Left precentral gyrus (SOM); 11= Left postcentral gyrus (SOM); 12= Left superior parietal lobule (DAN); 13= Left inferior parietal lobule (DMN); 14= Left supramarginal gyrus (VAN); 15= Left precuneus (DMN); 16= Left inferior occipital cortex (VIS); 17= Left calcarine (VIS); 18= Left cuneus (VIS); 19= Left lingual gyrus (VIS); 20= Left fusiform gyrus (DAN); 21= Left transverse temporal gyrus (SOM); 22= Left superior temporal gyrus (SOM); 23= Left middle temporal gyrus (DMN); 24= Left inferior temporal gyrus (LIM); 25= Left parahippocampal gyrus (LIM); 26= Left entorhinal cortex (LIM); 27= Left rostral anterior cingulate cortex (DMN); 28= Left caudal anterior cingulate cortex (VAN); 29= Left posterior cingulate cortex (FPN); 30= Left isthmus cingulate gyrus (DMN); 31= Left insula (VAN); 32= Right medial orbitofrontal gyrus (LIM); 33=

Right lateral orbitofrontal gyrus (LIM); 34= Right rostral middle frontal gyrus (FPN); 35= Right lateral frontal pars orbitalis (DMN); 36= Right superior frontal gyrus (DMN); 37= Right caudal middle frontal gyrus (FPN); 38= Right lateral frontal pars opercularis (FPN); 39= Right lateral frontal pars triangularis (FPN); 40= Right paracentral gyrus (SOM); 41= Right precentral gyrus (SOM); 42= Right postcentral gyrus (SOM); 43= Right superior parietal lobule (DAN); 44= Right inferior parietal lobule (DMN); 45= Right supramarginal gyrus (FPN); 46= Right precuneus (DMN); 47= Right inferior occipital cortex (VIS); 48= Right calcarine (VIS); 49= Right cuneus (VIS); 50= Right lingual gyrus (VIS); 51= Right fusiform gyrus (VIS); 52= Right transverse temporal gyrus (SOM); 53= Right superior temporal gyrus (SOM); 54= Right middle temporal gyrus (DMN); 55= Right inferior temporal gyrus (LIM); 56= Right parahippocampal gyrus (LIM); 57= Right entorhinal cortex (LIM); 58= Right rostral anterior cingulate cortex (DMN); 59= Right caudal anterior cingulate cortex (VAN); 60= Right posterior cingulate cortex (FPN); 61= Right isthmus cingulate gyrus (DMN); 62= Right insula (VAN); 63= Left hippocampal mammillary bodies; 64= Left hippocampal fornix; 65= Left hippocampal fimbria; 66= Left hippocampal CA1; 67= Left hippocampal subiculum; 68= Left hippocampal CA4/dentate gyrus; 69= Left hippocampal CA2/CA3; 70= Left hippocampal stratum radiatum, lacunosum, moleculare ; 71= Left hippocampal alveus; 72= Right hippocampal CA1; 73= Right hippocampal subiculum; 74= Right hippocampal CA4/dentate gyrus; 75= Right hippocampal CA2/CA3; 76= Right hippocampal stratum radiatum, lacunosum, moleculare; 77= Right hippocampal fimbria; 78= Right hippocampal mammillary bodies; 79= Right hippocampal fornix; 80= Right hippocampal alveus.
Associations illustrated are before correction for multiple comparisons. Grey links are non-significant associations. Purple links illustrate negative associations while orange links are for positive correlations. The width of links is proportional to the strength of the correlation.

2.4. Mediation models

We built mediation models to determine if there is an indirect association between BCs and functioning mediated by NS, controlling for age and sex. A pre-requisite of mediation models is a significant correlation between the mediator and the predictor as well as the mediator and the outcomes variable. In this case, it included significant BCs-NS, and NS-functioning associations. Based on results from 1.2, there is only a significant correlation between avolition and functional outcomes while avolition was significantly associated with the left calcarine (VIS), the left fusiform gyrus (DAN), the left middle temporal gyrus (DMN), the right transversal temporal gyrus (VAN), the left CA4/DG (hippocampus), the CA2/3 (hippocampus) and the right fornix (hippocampus). Therefore, we considered that avolition could be a proxy for our mediation model. The results of the mediation model are illustrated in Figure 8. The left middle temporal gyrus (DMN), the left CA4/DG, and the right fornix were the only structural BCs that predicted overall functioning, mediated by avolition. The rest of the models had significant total correlations between their BCs and overall functioning, but no significant indirect association through the NS.

Figure 8. Mediation models between BCs, avolition, and overall function controlling for age and sex.



*** Significant association**

CHAPTER 5: DISCUSSION

The aim of this thesis was to determine brain markers of NS as proxies of functional outcomes in FEP, applying a connectivity approach coupled with multimodal imaging BC measures. We expected NS to mediate the association between resting-state functionally-derived or structurally-derived BCs and functional deficits. We were able to construct mediation models in both modalities. In the first-study, looking at resting-state functional imaging of whole-brain networks, increased influence of most networks was associated with functional deficits. The high influence of the right hippocampus was indirectly predictive of functional deficits assessed with both SOFAS and GAF, an effect mediated by the SANS avolition/apathy. In the second study leveraging structural imaging and emphasizing networks hubs as well as hippocampal subfields, a general decrease of hub influence was observed across networks. The decrease of structural hub influence in the left middle temporal gyrus (DMN), the left CA4/DG, and the right fornix predicted lower functional outcomes on SOFAS mediated by the BNSS avolition. The results of each study will be discussed separately below. Thereafter, we will dive deeper into general observations.

1. Study 1: Resting-state Functional Connectivity in First-Episode Psychosis

Functional connectivity, defined as the temporal dependence of anatomically distinct regions with similar neuronal activity patterns measured by blood oxygen level-dependent (BOLD) signals, has provided insights into how healthy and impaired brains integrate and act on information at a large scale (Gur & Gur, 2010; Van den Heuvel & Hulshoff Pol, 2010). The goal of the first study was to apply a network perspective to investigate associations between functional outcomes, NS, and rs-fMRI BC in FEP. Our sample was clinically defined, as total scores of the SOFAS and GAF illustrated impaired functioning based on conventions in the field, and matched controls on age and sex, two variables shown to play a role in psychosis (Buck et al., 2020).

We observed a significant difference between the rs-fMRI BCs of FEP for the VIS, SOM, FPN, and DMN networks compared to BCs of controls. As expected, FEP had smaller BCs than controls. These results confirm the general decrease in connectivity observed in SZ and FEP as disrupted communication at large-scale results in functional impairments (Anderson & Cohen, 2013; del Fabro et al., 2021; Millan et al., 2014). However, rs-fMRI studies usually report differences for hub regions within networks. Our current comparison does not allow for a finer grain precision into regions to delineate the observed effects which is a limitation.

The LIM network showed larger BCs in FEP than in controls, but the effect was not significant. In a predictive study identifying hub regions of SZ compared to controls, regions with the LIM network and the hippocampus were found to be in the top ten hubs with the highest BCs (Cheng et al., 2015). The reorganization of network activity in those two regions, and specifically hyperactivity of the cortico-limbic connections, disrupt the emotional systems of the brain and directly impact levels of functioning in patients (Modinos et al., 2015). The LIM network thus has a different activity pattern supporting disruptions in functioning and NS as early as FEP which emphasize the importance of investigating connectivity in these areas.

1.1. Networks and clinical variables

Leveraging whole-brain networks allowed for an overall investigation of associations between brain connectivity and clinical variables. Increased BC measures, or hub influences, for all but the VIS network, were associated with lower functioning scores on the GAF and SOFAS scales. Functional outcomes comprise a variety of activities (e.g., social interactions, financial dependence, job-related skills) and are expected to involve multiple networks. The literature reports generalized disorganization involving altered hub influences in psychosis. A study with early-stage SZ showed high BC measures in the VIS and FPN networks in addition to subcortical

regions (Hummer et al., 2020). Another study focusing on the DMN found weaker connectivity between hubs such as the dorsal medial prefrontal cortex, the posterior cingulate cortex, and the precuneus in SZ individuals compared to controls but stronger connectivity between the temporal pole, medial motor cortex, and the anterior precuneus (Alonso-Solís et al., 2012). With abnormal hub influence increasing and decreasing in brain regions within networks, an effect impacted by antipsychotic treatment and severity of the disorder (Blessing et al., 2020; Chopra et al., 2021), there is a direct impact on the daily social and occupational functioning of individuals. Our observations show an increase in synchronous activity within networks to be associated with poor functioning. We suggest that due to the high connectivity of hubs with each other, an abnormal increase in brain activity would travel to other hubs compounding the disruption observed with our large-scale lens. Additionally, we may be observing a summation effect impacting the direction of the association and preventing the dissociation of more subtle finer grain hubs correlations.

With NS, a higher BC in the LIM network was associated significantly with a higher score on avolition/apathy. Abnormal LIM processing has been associated with NS relating to emotional flattening and social communication (White et al., 2008). The literature has provided a complex role for the LIM network, densely connected with the DMN, FPN, and subcortical areas. Reduced functional connectivity between the LIM network and other brain regions has been involved in emotional processing dysregulation in SZ while increased connectivity has been observed in regions usually not involved in emotional processing (Comte et al., 2018) which is observed in our findings. We suggest that abnormal activity of the LIM network directly impacts other systems as the memory and rewards circuitry which could underlie the association with avolition and apathy as a lack of motivation would subtend from the disruptions of anticipatory pleasure or recall of previous activities. Functional disruptions of the LIM network would also impact social contexts

recognition directly reducing the motivation to be in such contexts. The association between the LIM, avolition/apathy, and functional outcomes was subject to a mediation model which found no significant indirect association.

1.2. Hippocampus and clinical variables

The right hippocampus was indirectly associated with functional outcomes through avolition/apathy. This region converges the activity of many cortical networks, is important in memory, and although not directly implicated in the rewards network, the right hippocampus is active during rewards-related tasks but less stimulated in SZ patients (Mucci et al., 2015). Similar to the LIM network, the decreased recall of pleasure directly reduces motivation in pertaining activities resulting in functional deficits. The hippocampus has also shown direct structural associations with social cognition (Khalil et al., 2022) supporting its crucial role in amotivation as structure underlies brain function to some degree.

1.3. Limitations

The main limitation of this study pertains to the resolution issue referring to the lack of consensus in a field when investigating a variable with several levels and sub-levels. If the scope of the study is too broad, some associations are not uncovered due to a summation effect. If the scope of the study is too specific, it is difficult to extract generalized trends (Uddin et al., 2019). For BCs, we only used overall brain networks and the hippocampus to investigate functional connectivity. By nature, BC will reveal the influence of hubs on a network. The limitations in interpreting our results indicate that investigating brain regions within networks might be more appropriate to conclude which hubs are responsible for the general trends observed at a network level. This approach was utilized in a meta-analysis performed by the authors and yielded significant insights into which brain regions within networks were significantly associated with cognition in SZ (Khalil et al.,

2022). However, the scope of the thesis did not allow for a finer grain functional study as the investigation of networks hubs and hippocampal subfields were kept for the second study leveraging structural connectivity at ultra-high field resolution. Another limitation includes the absence of NS and functioning evaluations for controls which does not allow an appropriate comparison of groups especially for functional outcomes.

2. Study 2: Structural Connectivity in First-Episode Psychosis

Although constructing brain networks usually leverages functional activity, structural covariance is a method used to build a structural connectome from morphometric measures assuming that areas with similar architecture will be correlated and form a structural network (Alexander-Bloch et al., 2013; Evans, 2013). The goal of this chapter was to provide a fine grain peek into the influence of hubs, structural BC, associated with NS, and functional deficits. Leveraging high-resolution 7T neuroimaging allowed for a better delineation of networks hubs and hippocampal subfields while addressing the limitations of the first study. Our FEP and controls samples were matched on age, sex, and education level. FEP individuals had a significantly lower mean functioning score confirming that our sample was clinically defined and supporting the presence of significant functional impairments as early as in early psychosis (Conus, Cotton, Schimmelmann, McGorry, & Lambert, 2007; Crespo-Facorro et al., 2021).

For most hubs, the structural BC of FEP individuals was larger than those of controls, an effect significant for the left calcarine (VIS), left isthmus of the cingulate gyrus (DMN), right precentral gyrus (SOM), and right postcentral gyrus (SOM). In other words, the myelin composition of these hubs was increasingly similar to that of others in the networks in patients. We believe this effect to be mediated by a reduced diversity in neuronal composition in psychosis. Reduced connections, grey matter volume, and other morphometric hallmarks of a healthy brain would result in a

homogenous brain composition driving NS and functional deficits. Another proposition ties with the first study presented in this thesis. Reduced functional synchronous activity is observed in FEP compared to controls, and that is coupled with a structural reduction in volume reported in the literature. To compensate, neural integration of information is theorized to take alternative routes, resulting in an abnormal activity that is less synchronous in these "new routes" compared to controls but also resulting in the appearance of new structural regions with more control over information flow, aligning with the findings in the second study.

Concerning the hippocampus, the left subiculum was the only subregion with a significant difference between controls and FEP patients. The study by Makowski et al. (2020) showed a lower participation coefficient, a centrality measure assessing the distribution of a node in a network, in the CA1 and alveus bilaterally, the left subiculum the left fornix, and the right fimbria. Our results align with Makowski et al. (2020). The left subiculum is an important hub in FEP that has a reduced number of connections with nodes in other modules compared to its own module leading to an increased influence of the left subiculum as a hub in the left hippocampal module. It is a sensitive subfield that should be considered an early predictor of psychosis.

2.1. Networks and clinical variables

Functional deficits were significantly associated with the reduced influence of most hubs within networks. Less information passing through those nodes would support the literature in a general dysconnectivity hypothesis involving multiple networks and resulting in different clinical symptoms and functional deficits. These findings could be explained with the theory proposed above for group differences. The appearance of new structural hubs, more influential than in controls, but with an overall reduced influence within networks could underlie psychosis. Rs-fMRI

studies have indeed shown evidence of abnormal hubs appearance in psychosis (Bassett, Nelson, Mueller, Camchong, & Lim, 2012).

Some of the strongest associations between low BC and clinical hallmarks included reduced BC of the left fusiform gyrus (DAN) associated with functional deficits and increased avolition. The left fusiform gyrus is known for its function in facial recognition, a crucial dimension of social engagements. The literature reports a reduced volume of the fusiform gyrus in SZ (Kuo & Pogue-Geile, 2019) associated with severe deficits in emotional recognition (Jung et al., 2021) and difficulties in understanding social cues. The reduced importance of the left fusiform as a hub of the DAN is expected to strain social functioning in FEP and reduce motivation for social activities.

Reduced BC of the left superior temporal gyrus was significantly correlated with reduced overall functioning and increased distress in patients. Mainly responsible for auditory processing, disruptions in this region have been associated with hallucinations (Bandeira, Barouh, Bandeira, & Quarantini, 2021). Similarly, the right transversal temporal gyrus (VAN), also important in auditory processing, and the left calcarine (VIS), involved in higher-order visual processing, showed reduced influence in their respective networks. Hallucinations, auditory and visual, have been strongly correlated in the literature with distress and impaired normal life (Tsang et al., 2021). Impaired functioning by hallucinations, although a positive symptom, indirectly reduces the motivation and engagement for future activities of individuals with FEP and could underlie a more general role of amotivation in psychosis independently of its NS categorization.

The left middle temporal gyrus (DMN) has been characterized in the literature for its functions in auditory higher-order processing, relevant in social situations, and in semantic recall through intensive connections with the hippocampal-amygdala complex, hallmarks of memory formation and emotional processing (Hu et al., 2013; Kuroki et al., 2006). Worse EXP associated with

reduced influence of the left middle temporal gyrus on the DMN is expected. When constructing mediation models, we found that the reduced influence of the middle temporal gyrus on the DMN indirectly predicted functional outcomes through increased avolition. Although the DMN was not a significant mediation model in the first chapter, the investigation of the middle temporal gyrus as an individual hub allowed us to uncover its importance in FEP. This area has shown early signs of abnormality related to psychosis and could serve as an endophenotype (Hu et al., 2013).

Contrary to the general tendency, the right parahippocampal gyrus (LIM) showed increased influence associated with functional deficits. The right parahippocampal gyrus is densely connected to the hippocampus and serves as a gateway for memory formation and emotional processing. As early as clinical high-risk of SZ, patients show functional dysconnectivity between the right parahippocampal and other cortical regions as the temporal and somatomotor regions (Du et al., 2018). Structurally, the right parahippocampus has a reduced cortical thickness in SZ, a characteristic that allows patients identification (Liang et al., 2019). It is plausible that reduced connections between the right parahippocampus and cortical regions lead to its hub influence within the network and underlie disruptions in encoding and retrieving memory.

2.2. Hippocampus and clinical variables

A study by Makowski et al. (2020) investigated specifically the association between the hippocampus subfields, verbal memory, and NS. In the study, centrality is assessed with the participation coefficient, a measure of the distribution of a node's edges within its module. It was found that worse NS were associated with a general increase in intra-hippocampal connections compared to hippocampal-networks connections. In other words, decreased hippocampal centrality, and dysconnectivity of the hippocampus from other cortical networks were correlated

with NS, an effect mediated by verbal memory. Output sub-regions of the hippocampus, the subiculum, CA1, alveus, fimbria, and fornix, seemed to drive the observed reduced centrality.

In our study, reduced influence of the left CA4/DG and right subiculum were directly associated with worse MAP scores. Increased avolition was associated with reduced hub influence of the left CA4/DG, the left CA2/3, and the right fornix. Anhedonia and associability were negatively correlated with the right subiculum. These results align with the Makowski et al. (2020) study associating reduced centrality of hippocampal output sub-regions (i.e., subiculum, CA1, and fornix) with NS. The CA4/DG and CA2/3 two memory-related processing regions in the hippocampus (Molitor, Sherrill, Morton, Miller, & Preston, 2021) were not unexpectedly associated with NS. Indeed, reduced motivation is associated with working and verbal memory impairments in SZ (Amodio et al., 2017; Brébion, Bressan, Pilowsky, & David, 2009). The reduced influence of the left CA4/DG and right fornix indirectly predicts functional deficits, an effect mediated by increased avolition in FEP.

2.3. Limitations

We were not able to determine how significant our results are compared to controls. Performing a partial correlation between functional scores on SOFAS and BC measures would allow us to delineate specific hub differences between FEP and controls. Furthermore, the use of structural connectivity combined with functionally-derived Yeo et al. (2011) networks is still controversial. More research is needed to determine whether the structural and functional connectomes have overlapping similarities. Finally, the sample size is significantly larger for the FEP than for controls which influences our interpretations of group differences for structural hub influence.

3. Overall Discussion

3.1. Avolition: the negative symptom above all others

Avolition is a reduced motivation and desire to initiate and participate in goal-directed activities such as work, studies, hobbies, and social commitments (Foussias & Remington, 2010; Sauvé, Brodeur, Shah, & Lepage, 2019). This amotivation reduces engagement in social and occupational activities, directly and indirectly influencing functional outcomes, through the awareness of individuals' restrictions in functioning and frustration with impairments other symptoms bring to their lives (Strauss & Gold, 2016). Although other NS have all shown significant associations with overall functioning in SZ (Foussias & Remington, 2010; Sauvé et al., 2019), studies have shown a stronger and independent association between the avolition/apathy specifically and overall outcomes (Faerden et al., 2009; Kiang, Christensen, Remington, & Kapur, 2003). In FEP, avolition has been sufficient in identifying individuals' functional deficits in the next year (Hovington, Bodnar, Joober, Malla, & Lepage, 2012). The importance of avolition above all other NS is emphasized in our findings in two different studies and with two different NS scales. It is the symptom that has the most associations with functional deficits, drives correlations of the MAP domain with BC measures, and acts as a mediator between BC and functional outcomes. Thus, we put forward the idea that investigating NS at a symptom level in FEP seems to be the most holistic and sensitive manner to delineate associations with other hallmarks of the disorder.

Our findings also reinforce a model proposed earlier in the field where avolition is assumed to denote a lack of a general drive or a blunted sense of wanting (Foussias & Remington, 2010). In a social setting, avolition would be manifested as a reduced motivation for goal-directed activities that include speech. On an individual basis, the lack of drive would be associated with the EXP domain (Foussias et al., 2014; Foussias & Remington, 2010; Sauvé et al., 2019). Although

specific associations have been made with brain structures like the hippocampus, known for its connections with emotionally-relevant structures like the amygdala (Duan et al., 2021), the EXP domain has not been a hallmark of NS (Hovington et al., 2012). It is suggested that SZ patients have impairments in the outward expression of emotions and not the internal experience of the emotion (Foussias & Remington, 2010; Sauvé et al., 2019). As such, patients do not lack the hedonic "consummatory" response, the pleasure that people anticipate from future events, but the "anticipatory" response, the pleasure that people have at the thought of a future event (Strauss, Wilbur, Warren, August, & Gold, 2011). The reduced "anticipatory" pleasure of patients reduces the willingness and motivation to pursue goal-directed social and occupational activities thus correlating with avolition (Foussias & Remington, 2010; Sauvé et al., 2019). We suggest that interventions in FEP should therefore be directed towards re-establishing the motivation or drive of individuals. To date, only one intervention, the Positive Emotion Program for SZ has shown an increased and maintained level of positive emotions that positively impacts motivation and pleasure (Favrod et al., 2015). We believe that future studies should direct their attention to understanding avolition specifically as an early sensitive symptom of psychosis and treating this NS before it rapidly worsens functional outcomes.

3.2. Functional vs structural: do they overlap?

The field has been trying to answer the question if functional and structural imaging findings overlap for a long time (Alexander-Bloch et al., 2013; Bassett et al., 2008; Hu et al., 2017; Passingham et al., 2002; Uddin et al., 2019). We investigated both structural and functional centrality with BC, a measure of hub influence on a network. However, there are different interpretations for BC measures depending on the modality (Rubinov & Sporns, 2010). With resting-state functional centrality, BC assesses the influence of a hub region as measured by the

co-activation of other regions in the network at rest. The nodes with the higher BCs are the ones that have the most synchronized activity with other areas, making these nodes hub regions controlling the information passing in a network. The edges between nodes are the efficiency of information transfer (Bullmore & Sporns, 2009; Cheng et al., 2015; Rubinov & Sporns, 2010). With qT1 structural centrality, BC assesses the influence of a hub region as measured by the structural covariance of myelin content of the node. The nodes with the higher BCs are the ones that have the most myelin content similarities with other nodes which usually reflects more connections. The edges between represent the information transferred (Bullmore & Sporns, 2009; Makowski et al., 2020; Rubinov & Sporns, 2010). The use of BC as a measure of centrality is a strategy that has its limitations. BC relies on the assumption that the paths are always the shortest to a node (Rubinov & Sporns, 2010). However, this might not always be true which impacts the interpretation of the importance of a node in efficient information flow within a network (Bullmore & Sporns, 2009; Cheng et al., 2015; Rubinov & Sporns, 2010). Additionally, the different precision levels in the two studies (networks vs hubs) complicates the question of overlap.

Nonetheless, our findings provide a nuanced answer. The most influential networks, and hubs within networks, overlap in both studies and those include the DMN, DAN, FPN, and SOM. These networks are the ones with the most connectivity reported in the literature and confirm the large-scale dysconnectivity underlying SZ. But the direction of their influence and associations is inversed. We suggest that reduced hub centrality or importance in connectivity on a structural level in those networks as seen in the second study might impact how the brain remediates to this loss by increasing the activity of other nodes to compensate leading to our observations in the first study. Evidence for localized compensation of structural reduction or loss by functional overactivation has been reported in the brain during aging (Di, Rypma, & Biswal, 2014).

Future studies should supplement BC with additional measures of centrality such as node efficiency (i.e., the closer nodes are the more efficient the information flow) or participation coefficient (i.e., distribution of a node's edges within and between networks) which might improve the connectivity profile built. Additionally, by investigating at the same level of precision, within networks hubs, both modalities will build more comprehensive multimodal comparison models. Finally, we have to take into consideration that our sample is composed of patients with a FEP who have inherent heterogeneous structural, functional, and clinical abnormalities not always generalizable.

3.3. The creativity network: a circuitry for avolition

A recent study by Ren et al. (2020) shows an important role of the middle temporal gyrus and the hippocampus in the formation of new associations and creative concepts as they connect together. Creativity, requiring both novelty and usefulness, is suggested to result from the destruction of a familiar concept category and the creation of a new one (Luft, Zioga, Thompson, Banissy, & Bhattacharya, 2018). The hippocampus, responsible for episodic memory is involved in assessing the usefulness criterion of any new concept, and its dense associations with the medial temporal areas are suggested to underlie the generation of new alternatives to be assessed on usefulness (Ren et al., 2020). The connectivity with the middle temporal gyrus, important in different information processing circuits, has been found to be important for the creation of the new category and its integration in other processing modalities (i.e., semantic, problem-solving), strengthening the creative category by breaking the old concept category (Ren et al., 2020).

Although several studies have found overlap between genetic markers of creativity and psychotic disorders (Reddy, Ukrani, Indla, & Ukrani, 2018), the observed reduced structural BC in both the middle temporal gyrus and the hippocampus in FEP coupled with this proposed

creativity circuitry allow us to suggest an underlying circuit for avolition. An initially reduced ability to form new useful categories and associations, leading to less engagement with tasks at hand, a feeling of "being stuck" or incapable, ultimately results in avolition. This hypothesis would also explain early cognitive impairments observed in SZ as the inability to creatively problem-solve or efficiently form new memories. The connectivity between the middle temporal gyrus and the hippocampus circuitry should be the goal of future studies to understand the neurobiology underlying avolition and to potentially build a powerful FEP predictive model leveraging clinical and imaging markers.

FINAL CONCLUSION

Determining markers of functional outcomes is crucial in FEP as it allows better tailoring of early interventions, by targeting multiple factors influencing outcomes, and ultimately improving recovery. Clinically, avolition is a sensitive and independent NS predicting functional deficits as early as FEP and should be the target of interventions ultimately improving many inter-connected symptoms and functional deficits. Our work also shines a light on the resolution issue in NS suggesting a symptom-level precision and not a total scale score approach in FEP. Resting-state functional imaging allowed for a large-scale study showing the important influence of most of the Yeo et al. (2011) networks (DMN, DAN, FPN, LIM, SOM, VAN) and the hippocampus in functional deficits. The high functional influence of the right hippocampus was indirectly correlated with lower functional outcomes mediated by avolition. Structural imaging leveraged hub-level investigation of BC and found that reduced connectivity was associated with functional deficits and NS. Reduced structural influence of the left middle temporal gyrus on the DMN was a significant predictor of functional outcomes mediated by avolition. Output hippocampal subfields, the left CA4/DG and the right fornix, were also significant predictors of functional outcomes in FEP through avolition. Combining imaging modalities provided a nuanced interpretation for the overlap of the results but the mismatch of precision was a limitation and future studies should focus on investigating connectivity with supplemented measures of centrality. Finally, the middle temporal gyrus and the hippocampus underlie an endophenotypic circuit of psychosis that could explain several clinical hallmarks of the disorder.

SUPPLEMENTARY MATERIAL

Table S1. Partial correlations controlling for age and sex between overall functioning scores, negative symptoms, and functional BC measures for FEP patients.

	Affective Blunting	Alogia	Avolition/ Apathy	Anhedonia/ Associability	Total SANS	SOFAS	GAF
LH	-0.283	-0.184	0.047	-0.234	-0.152	-0.199	-0.253
RH	0.057	-0.156	**0.338**	0.145	0.212	-0.246	-0.088
VIS	0.117	-0.074	0.12	0.258	0.268	-0.208	-0.275
SOM	-0.107	-0.066	-0.037	-0.076	-0.075	-0.192	**-0.455**
DAN	-0.089	-0.194	0.264	0.061	0.092	**-0.529**	**-0.606**
VAN	0.17	-0.124	0.269	0.095	0.243	**-0.39**	**-0.499**
LIM	0.089	-0.13	**0.327**	0.212	0.208	**-0.376**	**-0.567**
FPN	-0.058	-0.03	0.268	0.163	0.141	**-0.355**	**-0.589**
DMN	0.097	-0.067	0.233	0.223	0.212	**-0.387**	**-0.562**
SOFAS	-0.206	0.086	**-0.748**	-0.295	-0.511		
GAF	0.003	0.018	**-0.406**	-0.103	-0.278		

Note: LH = left hippocampus; RH = right hippocampus; VIS = visual network; SOM = somatomotor network; DAN = dorsal attentional network; VAN = ventral attentional network; LIM = limbic network; FPN = frontoparietal control network; DMN = default mode network; SOFAS = Social and Occupational Functioning Assessment Scale; GAF = Global Assessment of Functioning. **Significant difference.**

Table S2. Partial correlations controlling for age and sex between overall functioning scores, negatives symptoms, and structural BC measures for FEP patients.

	Anhedonia	Distress	Associability	Avolition	Blunted Affect	Alogia	EXP	MAP	SOFAS
Left medial orbitofrontal gyrus (LIM)	-0.284	-0.006	-0.181	-0.142	-0.164	-0.197	-0.193	-0.228	0.022
Left lateral orbitofrontal gyrus (LIM)	-0.032	0.002	-0.044	-0.132	-0.063	0.122	0.014	-0.066	-0.028
Left rostral middle frontal gyrus (FPN)	-0.041	0.126	0.161	-0.043	-0.066	0.056	-0.017	0.025	0.068
Left lateral frontal pars orbitalis (DMN)	-0.087	0.074	-0.086	-0.065	-0.158	-0.036	-0.118	-0.074	0.113
Left superior frontal gyrus (DMN)	-0.114	-0.067	-0.156	-0.18	-0.215	-0.034	-0.153	-0.157	-0.007
Left caudal middle frontal gyrus (DMN)	-0.269	-0.084	-0.192	-0.238	-0.202	-0.131	-0.188	-0.261	0.151
Left lateral frontal pars opercularis (DMN)	0.008	-0.071	0.021	-0.15	-0.064	0.106	0.006	-0.044	0.232
Left lateral frontal pars triangularis (DMN)	0.007	-0.056	0.033	-0.013	-0.08	-0.058	-0.077	0.001	-0.012
Left paracentral gyrus (SOM)	0.039	0.102	0.05	-0.074	-0.097	-0.04	-0.08	0.023	-0.175
Left precentral gyrus (SOM)	-0.134	-0.02	-0.042	-0.262	-0.017	-0.045	-0.031	-0.156	-0.161
Left postcentral gyrus (SOM)	-0.074	0.101	0.029	-0.133	-0.039	-0.099	-0.069	-0.055	-0.015
Left superior parietal lobule (DAN)	0.113	0.057	0.028	-0.191	0.018	0.022	0.021	0.014	0.085
Left inferior parietal lobule (DMN)	-0.016	-0.088	0.002	-0.029	-0.005	-0.123	-0.058	-0.027	0.069
Left supramarginal gyrus (VAN)	-0.098	0.123	0.093	-0.084	-0.088	-0.046	-0.077	-0.033	0.052
Left precuneus (DMN)	-0.198	0.112	-0.104	-0.155	-0.177	-0.156	-0.183	-0.155	-0.142
Left inferior occipital cortex (VIS)	-0.119	-0.071	-0.138	-0.265	-0.025	0.01	-0.012	-0.18	0.26
Left calcarine (VIS)	-0.073	-0.255	-0.119	**-0.314**	0.147	-0.035	0.079	-0.19	**0.494**
Left cuneus (VIS)	-0.159	-0.121	-0.095	-0.226	0.098	0.255	0.177	-0.184	0.004
Left lingual gyrus (VIS)	-0.045	-0.167	-0.006	-0.096	0.053	0.001	0.035	-0.073	0.148
Left fusiform gyrus (DAN)	-0.172	-0.267	-0.226	**-0.324**	-0.023	-0.05	-0.037	-0.271	**0.488**
Left transverse temporal gyrus (SOM)	-0.073	-0.089	-0.067	-0.19	0.05	0.129	0.089	-0.12	0.174
Left superior temporal gyrus (SOM)	-0.099	**-0.332**	-0.139	-0.273	0.041	-0.122	-0.028	-0.206	**0.303**
Left middle temporal gyrus (DMN)	-0.173	-0.244	**-0.334**	**-0.337**	-0.241	**-0.308**	**-0.291**	**-0.301**	0.091
Left inferior temporal gyrus (LIM)	0.089	-0.17	-0.072	-0.207	-0.078	-0.039	-0.067	-0.057	**0.303**

Left parahippocampal gyrus (LIM)	-0.039	0.016	-0.12	-0.153	0.071	0.083	0.083	-0.093	-0.157
Left entorhinal cortex (LIM)	-0.062	-0.072	-0.073	-0.243	0.066	0.165	0.116	-0.129	0.084
Left rostral anterior cingulate cortex (DMN)	0.061	0.198	-0.022	-0.023	-0.038	-0.058	-0.05	0.042	-0.126
Left caudal anterior cingulate cortex (VAN)	-0.11	-0.026	-0.096	-0.09	-0.08	0.144	0.013	-0.108	0.096
Left posterior cingulate cortex (FPN)	-0.116	-0.035	-0.06	-0.049	-0.064	0.039	-0.024	-0.091	**0.29**
Left isthmus cingulate gyrus (DMN)	-0.196	0.125	-0.05	-0.089	-0.19	-0.136	-0.183	-0.119	0.256
Left insula (VAN)	-0.076	0.139	0.05	-0.004	-0.086	-0.025	-0.066	-0.008	0.103
Right medial orbitofrontal gyrus (LIM)	-0.05	0.174	-0.039	-0.057	-0.042	0.033	-0.012	-0.03	-0.107
Right lateral orbitofrontal gyrus (LIM)	-0.05	0.007	0.053	0.031	-0.05	0.021	-0.023	-0.001	0.154
Right rostral middle frontal gyrus (FPN)	-0.237	-0.028	-0.05	-0.104	-0.135	-0.12	-0.14	-0.163	0.194
Right lateral frontal pars orbitalis (DMN)	-0.098	0.104	0.054	-0.057	-0.086	0.045	-0.035	-0.038	0.119
Right superior frontal gyrus (DMN)	-0.056	0.181	0.008	-0.169	-0.008	0.116	0.046	-0.052	-0.002
Right caudal middle frontal gyrus (FPN)	-0.016	0.109	0.062	0.092	0.087	0.152	0.123	0.049	0.176
Right lateral frontal pars opercularis (FPN)	-0.086	-0.04	-0.081	-0.12	-0.203	-0.095	-0.173	-0.103	0.035
Right lateral frontal pars triangularis (FPN)	0.032	0.095	0.077	0.071	-0.004	0.048	0.019	0.068	**-0.304**
Right paracentral gyrus (SOM)	-0.009	0.134	0.161	0.108	-0.045	0.059	-0.003	0.086	-0.071
Right precentral gyrus (SOM)	-0.04	0.11	0.112	0.193	0.051	0.187	0.116	0.08	0.04
Right postcentral gyrus (SOM)	-0.282	-0.113	-0.125	-0.215	-0.069	0.104	0.002	-0.247	0.045
Right superior parietal lobule (DAN)	-0.03	0.052	-0.098	-0.197	-0.069	0.068	-0.014	-0.092	0.147
Right inferior parietal lobule (DMN)	-0.096	0.009	-0.1	-0.194	0.026	-0.181	-0.064	-0.128	0.271
Right supramarginal gyrus (FPN)	-0.277	-0.126	-0.281	-0.278	-0.186	-0.08	-0.155	**-0.306**	**0.291**
Right precuneus (DMN)	-0.224	0.004	-0.148	-0.069	-0.174	-0.196	-0.199	-0.168	0.067
Right inferior occipital cortex (VIS)	-0.025	0.064	0.107	-0.112	0.115	-0.135	0.014	-0.009	0.194
Right calcarine (VIS)	-0.089	-0.039	0.017	-0.157	0.093	-0.048	0.039	-0.09	0.234
Right cuneus (VIS)	-0.086	0.097	-0.017	-0.254	0.042	-0.03	0.013	-0.109	0.054
Right lingual gyrus (VIS)	0.182	0.043	0.125	-0.215	0.104	0.272	0.188	0.064	0.173
Right fusiform gyrus (VIS)	-0.198	-0.009	-0.124	-0.246	-0.073	-0.087	-0.085	-0.202	-0.04
Right transverse temporal gyrus (SOM)	0.007	-0.005	-0.049	**-0.308**	-0.113	-0.138	-0.134	-0.1	**0.331**

Right superior temporal gyrus (SOM)	-0.171	-0.063	-0.049	-0.201	-0.082	-0.117	-0.105	-0.163	0.073
Right middle temporal gyrus (DMN)	**-0.299**	-0.071	-0.212	-0.222	-0.215	-0.255	-0.252	-0.275	0.128
Right inferior temporal gyrus (LIM)	0.092	-0.126	0.105	-0.217	0.151	0.048	0.118	-0.007	0.261
Right parahippocampal gyrus (LIM)	0.013	0.132	0.082	-0.119	0.047	0.124	0.085	0.01	**-0.328**
Right entorhinal cortex (LIM)	-0.024	0.126	0.097	0.078	-0.07	0.071	-0.014	0.052	-0.101
Right rostral anterior cingulate cortex (DMN)	0.002	-0.073	0.141	-0.064	0.068	0.055	0.069	0.01	0.025
Right caudal anterior cingulate cortex (VAN)	-0.056	0.038	0.008	0.001	-0.119	0.024	-0.066	-0.02	-0.045
Right posterior cingulate cortex (FPN)	-0.015	0.135	0.077	0.059	-0.113	0.026	-0.061	0.047	0.19
Right isthmus cingulate gyrus (DMN)	-0.033	0.178	0.064	0.105	-0.045	-0.06	-0.055	0.054	0.171
Right insula (VAN)	-0.04	0.1	0.149	0.005	0.009	-0.062	-0.022	0.033	0.149
Left hippocampal mammillary bodies	-0.167	-0.017	-0.019	-0.09	-0.138	0.046	-0.068	-0.115	0.052
Left hippocampal fornix	-0.215	0.002	-0.143	-0.113	-0.078	-0.132	-0.109	-0.175	0.02
Left hippocampal fimbria	-0.136	0.181	-0.071	-0.02	0.039	0.022	0.035	-0.068	-0.065
Left hippocampal CA1	-0.153	-0.077	-0.244	-0.107	-0.123	-0.101	-0.123	-0.18	-0.032
Left hippocampal subiculum	-0.183	0.041	-0.076	-0.06	-0.018	0.035	0.004	-0.121	0.075
Left hippocampal CA4/dentate gyrus	-0.28	-0.034	-0.276	**-0.365**	-0.148	-0.111	-0.144	**-0.32**	0.27
Left hippocampal CA2/CA3	0.117	-0.001	0.174	**0.295**	0.218	0.227	0.241	0.189	-0.014
Left hippocampal SR/SL/SM	0.065	-0.071	0.017	0.157	0.147	0.174	0.172	0.073	0.155
Left hippocampal alveus	-0.009	-0.16	-0.02	0.092	-0.004	0.008	0.001	-0.003	-0.007
Right hippocampal CA1	-0.094	-0.202	-0.189	-0.022	-0.041	0.07	0.004	-0.127	0.186
Right hippocampal subiculum	**-0.326**	-0.226	**-0.308**	-0.267	-0.258	-0.212	-0.26	**-0.346**	0.15
Right hippocampal CA4/dentate gyrus	-0.264	-0.108	-0.144	-0.123	-0.257	-0.109	-0.214	-0.216	0.206
Right hippocampal CA2/CA3	-0.218	-0.143	-0.201	-0.121	-0.131	-0.078	-0.119	-0.212	0.189
Right hippocampal SR/SL/SM	-0.158	-0.127	-0.183	-0.201	-0.052	-0.067	-0.063	-0.199	**0.333**
Right hippocampal fimbria	-0.001	0.273	0.047	-0.09	0.1	-0.227	-0.037	0.019	0.164
Right hippocampal mammillary bodies	-0.092	-0.181	-0.222	-0.206	0.032	-0.009	0.017	-0.186	0.272
Right hippocampal fornix	-0.136	0.018	-0.225	**-0.323**	-0.179	-0.12	-0.168	-0.218	0.206
Right hippocampal alveus	-0.22	0.07	-0.101	-0.188	-0.018	-0.077	-0.046	-0.18	0.215

SOFAS	-0.06	-0.273	-0.263	**-0.336**	-0.085	-0.092	-0.096	-0.230	

Note: EXP = emotional expressivity; MAP = motivation and pleasure; SOFAS = Social and Occupational Functioning Assessment Scale. **Significant difference.**

REFERENCES

Ad-Dab'bagh, Y., Lyttelton, O., Muehlboeck, J., Lepage, C., Einarson, D., Mok, K., . . . Fombonne, E. (2006). *The CIVET image-processing environment: a fully automated comprehensive pipeline for anatomical neuroimaging research.* Paper presented at the Proceedings of the 12th annual meeting of the organization for human brain mapping.

Ahmed, A. O., Kirkpatrick, B., Granholm, E., Rowland, L. M., Barker, P. B., Gold, J. M., . . . Strauss, G. P. (2022). Two Factors, Five Factors, or Both? External Validation Studies of Negative Symptom Dimensions in Schizophrenia. *Schizophrenia Bulletin*, sbab148. doi:10.1093/schbul/sbab148

Ajnakina, O., Das, T., Lally, J., Di Forti, M., Pariante, C. M., Marques, T. R., . . . Dazzan, P. (2021). Structural Covariance of Cortical Gyrification at Illness Onset in Treatment Resistance: A Longitudinal Study of First-Episode Psychoses. *Schizophrenia Bulletin*. doi:10.1093/schbul/sbab035

Akudjedu, T. N., Tronchin, G., McInerney, S., Scanlon, C., Kenney, J. P. M., McFarland, J., . . . Hallahan, B. (2020). Progression of neuroanatomical abnormalities after first-episode of psychosis: A 3-year longitudinal sMRI study. *Journal of Psychiatric Research, 130*, 137-151. doi:https://doi.org/10.1016/j.jpsychires.2020.07.034

Alexander-Bloch, A. F., Vértes, P. E., Stidd, R., Lalonde, F., Clasen, L., Rapoport, J., . . . Gogtay, N. (2013). The anatomical distance of functional connections predicts brain network topology in health and schizophrenia. *Cerebral cortex, 23*(1), 127-138.

Alonso-Solís, A., Corripio, I., de Castro-Manglano, P., Duran-Sindreu, S., Garcia-Garcia, M., Proal, E., . . . Castellanos, F. X. (2012). Altered default network resting state functional connectivity in patients with a first episode of psychosis. *Schizophrenia Research, 139*(1), 13-18. doi:https://doi.org/10.1016/j.schres.2012.05.005

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.).

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. Vol. 152): American Psychiatric Publishing.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.).

Amodio, A., Quarantelli, M., Mucci, A., Prinster, A., Soricelli, A., Vignapiano, A., . . . Galderisi, S. (2017). Avolition-Apathy and White Matter Connectivity in Schizophrenia: Reduced Fractional Anisotropy Between Amygdala and Insular Cortex. *Clinical EEG and Neuroscience, 49*(1), 55-65. doi:10.1177/1550059417745934

Anderson, A., & Cohen, M. S. (2013). Decreased small-world functional network connectivity and clustering across resting state networks in schizophrenia: an fMRI classification tutorial. *Frontiers in human neuroscience, 7*, 520.

Andreasen, N. C. (1989). The Scale for the Assessment of Negative Symptoms (SANS): Conceptual and Theoretical Foundations. *British Journal of Psychiatry, 155*(S7), 49-52. doi:10.1192/S0007125000291496

Andreasen, N. C., Carpenter, W. T., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *American Journal of Psychiatry, 162*(3), 441-449.

Ang, M. S., Rekhi, G., & Lee, J. (2019). Validation of the Brief Negative Symptom Scale and its association with functioning. *Schizophrenia Research, 208*, 97-104. doi:https://doi.org/10.1016/j.schres.2019.04.005

Antoniades, M., Schoeler, T., Radua, J., Valli, I., Allen, P., Kempton, M. J., & McGuire, P. (2018). Verbal learning and hippocampal dysfunction in schizophrenia: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 86*, 166-175. doi:https://doi.org/10.1016/j.neubiorev.2017.12.001

Bandeira, I. D., Barouh, J. L., Bandeira, I. D., & Quarantini, L. (2021). Analysis of the superior temporal gyrus as a possible biomarker in schizophrenia using voxel-based morphometry of the brain magnetic resonance imaging: a comprehensive review. *CNS Spectrums, 26*(4), 319-325. doi:10.1017/S1092852919001810

Bassett, D. S., Bullmore, E., Verchinski, B. A., Mattay, V. S., Weinberger, D. R., & Meyer-Lindenberg, A. (2008). Hierarchical Organization of Human Cortical Networks in Health and Schizophrenia. *The Journal of Neuroscience, 28*(37), 9239. doi:10.1523/JNEUROSCI.1929-08.2008

Bassett, D. S., Nelson, B. G., Mueller, B. A., Camchong, J., & Lim, K. O. (2012). Altered resting state complexity in schizophrenia. *Neuroimage, 59*(3), 2196-2207.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological), 57*(1), 289-300. doi:https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Benoit, A., Bodnar, M., Malla, A., Joober, R., & Lepage, M. (2012). The Structural Neural Substrates of Persistent Negative Symptoms in First-Episode of Non-Affective Psychosis: A Voxel-Based Morphometry Study. *Frontiers in Psychiatry, 3*. doi:10.3389/fpsyt.2012.00042

Blanchard, J. J., & Cohen, A. S. (2006). The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophrenia Bulletin, 32*(2), 238-245.

Blessing, E. M., Murty, V. P., Zeng, B., Wang, J., Davachi, L., & Goff, D. C. (2020). Anterior Hippocampal–Cortical Functional Connectivity Distinguishes Antipsychotic Naïve First-Episode Psychosis Patients From Controls and May Predict Response to Second-Generation Antipsychotic Treatment. *Schizophrenia Bulletin, 46*(3), 680-689. doi:10.1093/schbul/sbz076

Bowie, C. R., Leung, W. W., Reichenberg, A., McClure, M. M., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2008). Predicting Schizophrenia Patients' Real-World Behavior with Specific Neuropsychological and Functional Capacity Measures. *Biological Psychiatry, 63*(5), 505-511. doi:https://doi.org/10.1016/j.biopsych.2007.05.022

Brant-Zawadzki, M., Gillan, G. D., & Nitz, W. R. (1992). MP RAGE: a three-dimensional, T1-weighted, gradient-echo sequence--initial experience in the brain. *Radiology, 182*(3), 769-775.

Brébion, G., Bressan, R. A., Pilowsky, L. S., & David, A. S. (2009). Depression, Avolition, and Attention Disorders in Patients with Schizophrenia: Associations with Verbal Memory Efficiency. *The Journal of Neuropsychiatry and Clinical Neurosciences, 21*(2), 206-215. doi:10.1176/jnp.2009.21.2.206

Brissos, S., Molodynski, A., Dias, V. V., & Figueira, M. L. (2011). The importance of measuring psychosocial functioning in schizophrenia. *Annals of General Psychiatry, 10*(1), 18. doi:10.1186/1744-859X-10-18

Bromley, E., & Brekke, J. S. (2010). Assessing Function and Functional Outcome in Schizophrenia. In N. R. Swerdlow (Ed.), *Behavioral Neurobiology of Schizophrenia and Its Treatment* (pp. 3-21). Berlin, Heidelberg: Springer Berlin Heidelberg.

Buck, G., Lavigne, K. M., Makowski, C., Joober, R., Malla, A., & Lepage, M. (2020). Sex Differences in Verbal Memory Predict Functioning Through Negative Symptoms in Early Psychosis. *Schizophrenia Bulletin, 46*(6), 1587-1595. doi:10.1093/schbul/sbaa054

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature reviews neuroscience, 10*(3), 186-198.

Catts, S. V., Frost, A. D., O'Toole, B. I., Carr, V. J., Lewin, T., Neil, A. L., . . . Eadie, K. (2011). Clinical indicators for routine use in the evaluation of early psychosis intervention: development, training support and inter-rater reliability. *Australian & New Zealand Journal of Psychiatry, 45*(1), 63-75.

Cheng, H., Newman, S., Goñi, J., Kent, J. S., Howell, J., Bolbecker, A., . . . Hetrick, W. P. (2015). Nodal centrality of functional network in the differentiation of schizophrenia. *Schizophrenia Research, 168*(1), 345-352. doi:https://doi.org/10.1016/j.schres.2015.08.011

Chopra, S., Francey, S. M., O'Donoghue, B., Sabaroedin, K., Arnatkeviciute, A., Cropley, V., . . . Fornito, A. (2021). Functional Connectivity in Antipsychotic-Treated and Antipsychotic-Naive Patients With First-Episode Psychosis and Low Risk of Self-harm or Aggression: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Psychiatry, 78*(9), 994-1004. doi:10.1001/jamapsychiatry.2021.1422

Compton, M. (2008). Incorporating the Prevention Paradigm into Administrative Psychiatry. *Psychiatric Clinics of North America, 31*(1), 73-84. doi:https://doi.org/10.1016/j.psc.2007.11.004

Compton, M., McGlashan, T., & McGorry, P. (2007). Toward Prevention Approaches for Schizophrenia: An Overview of Prodromal States, the Duration of Untreated Psychosis, and Early Intervention Paradigms. *Psychiatric Annals, 37*(5), 340-348. Retrieved from https://proxy.library.mcgill.ca/login?url=https://www.proquest.com/scholarly-journals/toward-prevention-approaches-schizophrenia/docview/217059906/se-2?accountid=12339

https://mcgill.on.worldcat.org/atoztitles/link?sid=ProQ:&issn=00485713&volume=37&issue=5&title=Toward+Prevention+Approaches+for+Schizophrenia%3A+An+Overview+of+Prodromal+States%2C+the+Duration+of+Untreated+Psychosis%2C+and+Early+Intervention+Paradigms&spage=340&date=2007&atitle=Toward+Prevention+Approaches+for+Schizophrenia%3A+An+Overview+of+Prodromal+States%2C+the+Duration+of+Untreated+Psychosis%2C+and+Early+Intervention+Paradigms&au=Compton%2C+Michael+T%2C+MD%2C+MPH%3BMcGlashan%2C+Thomas+H%2C+MD%3BMcGorry%2C+Patrick+D%2C+MD&id=&isbn=

Comte, M., Zendjidjian, X. Y., Coull, J. T., Cancel, A., Boutet, C., Schneider, F. C., . . . Fakra, E. (2018). Impaired cortico-limbic functional connectivity in schizophrenia patients during emotion processing. *Social Cognitive and Affective Neuroscience, 13*(4), 381-390. doi:10.1093/scan/nsx083

Conus, P., Cotton, S., Schimmelmann, B. G., McGorry, P. D., & Lambert, M. (2007). The First-Episode Psychosis Outcome Study: premorbid and baseline characteristics of an epidemiological cohort of 661 first-episode psychosis patients. *Early intervention in psychiatry, 1*(2), 191-200. doi:https://doi.org/10.1111/j.1751-7893.2007.00026.x

Crespo-Facorro, B., Such, P., Nylander, A.-G., Madera, J., Resemann, H. K., Worthington, E., . . . Newton, R. (2021). The burden of disease in early schizophrenia – a systematic

literature review. *Current Medical Research and Opinion, 37*(1), 109-121. doi:10.1080/03007995.2020.1841618

Dama, M., Shah, J., Norman, R., Iyer, S., Joober, R., Schmitz, N., . . . Malla, A. (2019). Short duration of untreated psychosis enhances negative symptom remission in extended early intervention service for psychosis. *Acta Psychiatrica Scandinavica, 140*(1), 65-76. doi:https://doi.org/10.1111/acps.13033

Dama, M., Veru, F., Schmitz, N., Shah, J., Iyer, S., Joober, R., & Malla, A. (2019). Sex Differences in Clinical and Functional Outcomes among Patients Treated in an Early Intervention Service for Psychotic Disorders: An Observational Study. *The Canadian Journal of Psychiatry, 64*(10), 708-717. doi:10.1177/0706743719854069

Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure and Function, 213*(6), 525-533. doi:10.1007/s00429-009-0208-6

Das, T., Borgwardt, S., Hauke, D. J., Harrisberger, F., Lang, U. E., Riecher-Rössler, A., . . . Schmidt, A. (2018). Disorganized Gyrification Network Properties During the Transition to Psychosis. *JAMA Psychiatry, 75*(6), 613-622. doi:10.1001/jamapsychiatry.2018.0391

De Martino, F., Yacoub, E., Kemper, V., Moerel, M., Uludağ, K., De Weerd, P., . . . Formisano, E. (2018). The impact of ultra-high field MRI on cognitive and computational neuroimaging. *Neuroimage, 168*, 366-382. doi:https://doi.org/10.1016/j.neuroimage.2017.03.060

De Silva, J., Hanwella, R., & De Silva, V. (2012). Direct and indirect cost of schizophrenia in outpatients treated in a tertiary care psychiatry unit. *Ceylon Medical Journal, 57*(1).

del Fabro, L., Schmidt, A., Fortea, L., Delvecchio, G., D'Agostino, A., Radua, J., . . . Brambilla, P. (2021). Functional brain network dysfunctions in subjects at high-risk for psychosis: A meta-analysis of resting-state functional connectivity. *Neuroscience & Biobehavioral Reviews, 128*, 90-101. doi:https://doi.org/10.1016/j.neubiorev.2021.06.020

Dempster, K., Jeon, P., MacKinley, M., Williamson, P., Théberge, J., & Palaniyappan, L. (2020). Early treatment response in first episode psychosis: a 7-T magnetic resonance spectroscopic study of glutathione and glutamate. *Molecular Psychiatry, 25*(8), 1640-1650. doi:10.1038/s41380-020-0704-x

Di, X., Rypma, B., & Biswal, B. B. (2014). Correspondence of executive function related functional and anatomical alterations in aging brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 48*, 41-50. doi:https://doi.org/10.1016/j.pnpbp.2013.09.001

Dong, D., Wang, Y., Chang, X., Luo, C., & Yao, D. (2018). Dysfunction of Large-Scale Brain Networks in Schizophrenia: A Meta-analysis of Resting-State Functional Connectivity. *Schizophrenia Bulletin, 44*(1), 168-181. doi:10.1093/schbul/sbx034

Du, Y., Fryer, S. L., Fu, Z., Lin, D., Sui, J., Chen, J., . . . Calhoun, V. D. (2018). Dynamic functional connectivity impairments in early schizophrenia and clinical high-risk for psychosis. *Neuroimage, 180*, 632-645. doi:https://doi.org/10.1016/j.neuroimage.2017.10.022

Duan, X., He, C., Ou, J., Wang, R., Xiao, J., Li, L., . . . Chen, H. (2021). Reduced Hippocampal Volume and Its Relationship With Verbal Memory and Negative Symptoms in Treatment-Naive First-Episode Adolescent-Onset Schizophrenia. *Schizophrenia Bulletin, 47*(1), 64-74. doi:10.1093/schbul/sbaa092

Eggenschwiler, F., Kober, T., Magill, A. W., Gruetter, R., & Marques, J. P. (2012). SA2RAGE: A new sequence for fast B1+-mapping. *Magnetic Resonance in Medicine, 67*(6), 1609-1619. doi:https://doi.org/10.1002/mrm.23145

Esteban, O., Birman, D., Schaer, M., Koyejo, O. O., Poldrack, R. A., & Gorgolewski, K. J. (2017). MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites. *PLOS ONE, 12*(9), e0184661. doi:10.1371/journal.pone.0184661

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., . . . Snyder, M. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature methods, 16*(1), 111-116.

Evans, A. C. (2013). Networks of anatomical covariance. *Neuroimage, 80*, 489-504.

Faerden, A., Friis, S., Agartz, I., Barrett, E. A., Nesvåg, R., Finset, A., & Melle, I. (2009). Apathy and Functioning in First-Episode Psychosis. *Psychiatric Services, 60*(11), 1495-1503. doi:10.1176/ps.2009.60.11.1495

Falakshahi, H., Vergara, V. M., Liu, J., Mathalon, D. H., Ford, J. M., Voyvodic, J., . . . Calhoun, V. D. (2020). Meta-Modal Information Flow: A Method for Capturing Multimodal Modular Disconnectivity in Schizophrenia. *IEEE Transactions on Biomedical Engineering, 67*(9), 2572-2584. doi:10.1109/TBME.2020.2964724

Favrod, J., Nguyen, A., Fankhauser, C., Ismailaj, A., Hasler, J.-D., Ringuet, A., . . . Bonsack, C. (2015). Positive Emotions Program for Schizophrenia (PEPS): a pilot intervention to reduce anhedonia and apathy. *BMC Psychiatry, 15*(1), 231. doi:10.1186/s12888-015-0610-y

Foussias, G., Agid, O., Fervaha, G., & Remington, G. (2014). Negative symptoms of schizophrenia: clinical features, relevance to real world functioning and specificity versus other CNS disorders. *European Neuropsychopharmacology, 24*(5), 693-709.

Foussias, G., & Remington, G. (2010). Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophrenia Bulletin, 36*(2), 359-369.

Friston, K., Brown, H. R., Siemerkus, J., & Stephan, K. E. (2016a). The dysconnection hypothesis (2016). *Schizophrenia Research, 176*(2-3), 83-94.

Friston, K., Brown, H. R., Siemerkus, J., & Stephan, K. E. (2016b). The dysconnection hypothesis (2016). *Schizophrenia Research, 176*(2), 83-94. doi:https://doi.org/10.1016/j.schres.2016.07.014

Galderisi, S., Mucci, A., Dollfus, S., Nordentoft, M., Falkai, P., Kaiser, S., . . . Gaebel, W. (2021). EPA guidance on assessment of negative symptoms in schizophrenia. *European Psychiatry, 64*(1), e23. doi:10.1192/j.eurpsy.2021.11

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., . . . Jenkinson, M. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage, 80*, 105-124. doi:https://doi.org/10.1016/j.neuroimage.2013.04.127

González-Vivas, C., Soldevila-Matías, P., Sparano, O., García-Martí, G., Martí-Bonmatí, L., Crespo-Facorro, B., . . . Sanjuan, J. (2019). Longitudinal studies of functional magnetic resonance imaging in first-episode psychosis: A systematic review. *European Psychiatry, 59*, 60-69. doi:10.1016/j.eurpsy.2019.04.009

Gould, F., Bowie, C. R., & Harvey, P. D. (2012). The influence of demographic factors on functional capacity and everyday functional outcomes in schizophrenia. *Journal of Clinical and Experimental Neuropsychology, 34*(5), 467-475. doi:10.1080/13803395.2011.651102

Gur, R. E., & Gur, R. C. (2010). Functional magnetic resonance imaging in schizophrenia. *Dialogues in clinical neuroscience, 12*(3), 333.
Gutman, B. A., van Erp, T. G. M., Alpert, K., Ching, C. R. K., Isaev, D., Ragothaman, A., . . . Wang, L. (2022). A meta-analysis of deep brain structural shape and asymmetry abnormalities in 2,833 individuals with schizophrenia compared with 3,929 healthy volunteers via the ENIGMA Consortium. *Human Brain Mapping, 43*(1), 352-372. doi:https://doi.org/10.1002/hbm.25625
Harvey, P. D., & Strassnig, M. (2012). Predicting the severity of everyday functional disability in people with schizophrenia: cognitive deficits, functional capacity, symptoms, and health status. *World psychiatry : official journal of the World Psychiatric Association (WPA), 11*(2), 73-79. doi:10.1016/j.wpsyc.2012.05.004
Hayes, A. F. (2012). PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling. In: University of Kansas, KS.
Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*: Guilford publications.
Hollingshead, A. B. (1957). Two factor index of social position.
Hovington, C. L., Bodnar, M., Joober, R., Malla, A. K., & Lepage, M. (2012). Identifying persistent negative symptoms in first episode psychosis. *BMC Psychiatry, 12*(1), 224. doi:10.1186/1471-244X-12-224
Hovington, C. L., & Lepage, M. (2012). Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. *Expert Review of Neurotherapeutics, 12*(1), 53-69. doi:10.1586/ern.11.173
Hu, M., Li, J., Eyler, L., Guo, X., Wei, Q., Tang, J., . . . Zhao, J. (2013). Decreased left middle temporal gyrus volume in antipsychotic drug-naive, first-episode schizophrenia patients and their healthy unaffected siblings. *Schizophrenia Research, 144*(1), 37-42. doi:https://doi.org/10.1016/j.schres.2012.12.018
Hu, M., Zong, X.-F., Mann, J. J., Zheng, J.-J., Liao, Y.-H., Li, Z.-C., . . . Tang, J.-S. (2017). A Review of the Functional and Anatomical Default Mode Network in Schizophrenia. *Neuroscience Bulletin, 33*(1), 73-84. doi:10.1007/s12264-016-0090-1
Hummer, T. A., Yung, M. G., Goñi, J., Conroy, S. K., Francis, M. M., Mehdiyoun, N. F., & Breier, A. (2020). Functional network connectivity in early-stage schizophrenia. *Schizophrenia Research, 218*, 107-115. doi:https://doi.org/10.1016/j.schres.2020.01.023
Huntenburg, J. M., Bazin, P.-L., Goulas, A., Tardif, C. L., Villringer, A., & Margulies, D. S. (2017). A systematic relationship between functional connectivity and intracortical myelin in the human cerebral cortex. *Cerebral cortex, 27*(2), 981-997.
IBMCorp. (2020). IBM SPSS Statistics (Version 27.0).
Iyer, S., Jordan, G., MacDonald, K., Joober, R., & Malla, A. (2015). Early Intervention for Psychosis: A Canadian Perspective. *The Journal of Nervous and Mental Disease, 203*(5). Retrieved from https://journals.lww.com/jonmd/Fulltext/2015/05000/Early_Intervention_for_Psychosis__A_Canadian.9.aspx
James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., . . . Abdelalim, A. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet, 392*(10159), 1789-1858.

Juckel, G., Schaub, D., Fuchs, N., Naumann, U., Uhl, I., Witthaus, H., . . . Brüne, M. (2008). Validation of the Personal and Social Performance (PSP) Scale in a German sample of acutely ill patients with schizophrenia. *Schizophrenia Research, 104*(1), 287-293. doi:https://doi.org/10.1016/j.schres.2008.04.037

Jung, S., Kim, J.-H., Kang, N.-O., Sung, G., Ko, Y.-G., Bang, M., . . . Lee, S.-H. (2021). Fusiform gyrus volume reduction associated with impaired facial expressed emotion recognition and emotional intensity recognition in patients with schizophrenia spectrum psychosis. *Psychiatry Research: Neuroimaging, 307*, 111226. doi:https://doi.org/10.1016/j.pscychresns.2020.111226

Kahn, R. S., Sommer, I. E., Murray, R. M., Meyer-Lindenberg, A., Weinberger, D. R., Cannon, T. D., . . . Insel, T. R. (2015). Schizophrenia. *Nat Rev Dis Primers, 1*, 15067. doi:10.1038/nrdp.2015.67

Khalil, M., Hollander, P., Raucher-Chéné, D., Lepage, M., & Lavigne, K. M. (2022). Structural brain correlates of cognitive function in schizophrenia: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 132*, 37-49.

Kiang, M., Christensen, B. K., Remington, G., & Kapur, S. (2003). Apathy in schizophrenia: clinical correlates and association with functional outcome. *Schizophrenia Research, 63*(1), 79-88. doi:https://doi.org/10.1016/S0920-9964(02)00433-4

Kirkpatrick, B., Fenton, W. S., Carpenter, W. T., & Marder, S. R. (2006). The NIMH-MATRICS consensus statement on negative symptoms. *Schizophrenia Bulletin, 32*(2), 214-219.

Kirkpatrick, B., Strauss, G. P., Nguyen, L., Fischer, B. A., Daniel, D. G., Cienfuegos, A., & Marder, S. R. (2011). The Brief Negative Symptom Scale: Psychometric Properties. *Schizophrenia Bulletin, 37*(2), 300-305. doi:10.1093/schbul/sbq059

Kirschner, M., Schmidt, A., Hodzic-Santor, B., Burrer, A., Manoliu, A., Zeighami, Y., . . . Kaiser, S. (2021). Orbitofrontal-Striatal Structural Alterations Linked to Negative Symptoms at Different Stages of the Schizophrenia Spectrum. *Schizophrenia Bulletin, 47*(3), 849-863. doi:10.1093/schbul/sbaa169

Kirschner, M., Shafiei, G., Markello, R. D., Makowski, C., Talpalaru, A., Hodzic-Santor, B., . . . Lepage, M. (2020). Latent clinical-anatomical dimensions of schizophrenia. *Schizophrenia Bulletin, 46*(6), 1426-1438.

Klein, A., & Tourville, J. (2012). 101 Labeled Brain Images and a Consistent Human Cortical Labeling Protocol. *Frontiers in Neuroscience, 6*(171). doi:10.3389/fnins.2012.00171

Krukow, P., Jonak, K., Karpiński, R., & Karakuła-Juchnowicz, H. (2019). Abnormalities in hubs location and nodes centrality predict cognitive slowing and increased performance variability in first-episode schizophrenia patients. *Scientific reports, 9*(1), 9594. doi:10.1038/s41598-019-46111-0

Kumari, S., Malik, M., Florival, C., Manalai, P., & Sonje, S. (2017). An Assessment of Five (PANSS, SAPS, SANS, NSA-16, CGI-SCH) commonly used Symptoms Rating Scales in Schizophrenia and Comparison to Newer Scales (CAINS, BNSS). *Journal of addiction research & therapy, 8*(3), 324. doi:10.4172/2155-6105.1000324

Kuo, S. S., & Pogue-Geile, M. F. (2019). Variation in fourteen brain structure volumes in schizophrenia: A comprehensive meta-analysis of 246 studies. *Neuroscience & Biobehavioral Reviews, 98*, 85-94. doi:https://doi.org/10.1016/j.neubiorev.2018.12.030

Kuroki, N., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Onitsuka, T., Ersner, H., . . . McCarley, R. W. (2006). Middle and Inferior Temporal Gyrus Gray Matter Volume

Abnormalities in First-Episode Schizophrenia: An MRI Study. *American Journal of Psychiatry, 163*(12), 2103-2110. doi:10.1176/ajp.2006.163.12.2103

Lavigne, K. M., Raucher-Chéné, D., Bodnar, M., Makowski, C., Joober, R., Malla, A., . . . Lepage, M. (2022 (submitted)). Medial temporal lobe and basal ganglia volume trajectories in persistent negative symptoms following a first episode of psychosis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*.

Lehman, A. F. (1983). The effects of psychiatric symptoms on quality of life assessments among the chronic mentally ill. *Evaluation and Program Planning, 6*(2), 143-151.

Lepage, M., Bodnar, M., & Bowie, C. R. (2014). Neurocognition: Clinical and Functional Outcomes in Schizophrenia. *The Canadian Journal of Psychiatry, 59*(1), 5-12. doi:10.1177/070674371405900103

Lepage, M., Bodnar, M., Raucher-Chéné, D., Lavigne, K. M., Makowski, C., Joober, R., & Malla, A. K. (2021). Neurocognitive functions in persistent negative symptoms following a first episode of psychosis. *European Neuropsychopharmacology, 47*, 86-97. doi:https://doi.org/10.1016/j.euroneuro.2021.02.008

Liang, S., Li, Y., Zhang, Z., Kong, X., Wang, Q., Deng, W., . . . Li, T. (2019). Classification of First-Episode Schizophrenia Using Multimodal Brain Features: A Combined Structural and Diffusion Imaging Study. *Schizophrenia Bulletin, 45*(3), 591-599. doi:10.1093/schbul/sby091

Limongi, R., Jeon, P., Théberge, J., & Palaniyappan, L. (2021). Counteracting Effects of Glutathione on the Glutamate-Driven Excitation/Inhibition Imbalance in First-Episode Schizophrenia: A 7T MRS and Dynamic Causal Modeling Study. *Antioxidants, 10*(1), 75. Retrieved from https://www.mdpi.com/2076-3921/10/1/75

London Health Sciences Centre. (2022). PEPP. Retrieved from https://www.lhsc.on.ca/pepp-prevention-and-early-intervention-program-for-psychoses/pepp

Luft, C. D. B., Zioga, I., Thompson, N. M., Banissy, M. J., & Bhattacharya, J. (2018). Right temporal alpha oscillations as a neural mechanism for inhibiting obvious associations. *proceedings of the National Academy of Sciences, 115*(52), E12144-E12152.

Lutgens, D., Joober, R., Iyer, S., Lepage, M., Norman, R., Schmitz, N., . . . Malla, A. (2019). Progress of negative symptoms over the initial 5 years of a first episode of psychosis. *Psychological Medicine, 49*(1), 66-74.

Lynn, C. W., & Bassett, D. S. (2019). The physics of brain network structure, function and control. *Nature Reviews Physics, 1*(5), 318-332. doi:10.1038/s42254-019-0040-8

Makowski, C., Bodnar, M., Malla, A. K., Joober, R., & Lepage, M. (2016). Age-related cortical thickness trajectories in first episode psychosis patients presenting with early persistent negative symptoms. *npj Schizophrenia, 2*(1), 16029. doi:10.1038/npjschz.2016.29

Makowski, C., Lewis, J. D., Khundrakpam, B., Tardif, C. L., Palaniyappan, L., Joober, R., . . . Lepage, M. (2020). Altered hippocampal centrality and dynamic anatomical covariance of intracortical microstructure in first episode psychosis. *Hippocampus, 30*(10), 1058-1072. doi:https://doi.org/10.1002/hipo.23215

Makowski, C., Lewis, J. D., Lepage, C., Malla, A. K., Joober, R., Lepage, M., & Evans, A. C. (2019). Structural associations of cortical contrast and thickness in first episode psychosis. *Cerebral cortex, 29*(12), 5009-5021.

Mann, H. B., & Whitney, D. R. (1947). On a test of whether one of two random variables is stochastically larger than the other. *The annals of mathematical statistics*, 50-60.

Marder, S. R., & Galderisi, S. (2017). The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry, 16*(1), 14-24. doi:https://doi.org/10.1002/wps.20385
Marques, J. P., Kober, T., Krueger, G., van der Zwaag, W., Van de Moortele, P.-F., & Gruetter, R. (2010). MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. *Neuroimage, 49*(2), 1271-1281. doi:https://doi.org/10.1016/j.neuroimage.2009.10.002
Martin, J. B. (2002). The Integration of Neurology, Psychiatry, and Neuroscience in the 21st Century. *American Journal of Psychiatry, 159*(5), 695-704. doi:10.1176/appi.ajp.159.5.695
MathWorks. (2021). MATLAB (Version R2021a).
McHugo, M., Armstrong, K., Roeske, M. J., Woodward, N. D., Blackford, J. U., & Heckers, S. (2020). Hippocampal volume in early psychosis: a 2-year longitudinal study. *Translational Psychiatry, 10*(1), 306. doi:10.1038/s41398-020-00985-1
Millan, M. J., Fone, K., Steckler, T., & Horan, W. P. (2014). Negative symptoms of schizophrenia: Clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. *European Neuropsychopharmacology, 24*(5), 645-692. doi:https://doi.org/10.1016/j.euroneuro.2014.03.008
Millier, A., Schmidt, U., Angermeyer, M. C., Chauhan, D., Murthy, V., Toumi, M., & Cadi-Soussi, N. (2014). Humanistic burden in schizophrenia: A literature review. *Journal of Psychiatric Research, 54*, 85-93. doi:https://doi.org/10.1016/j.jpsychires.2014.03.021
Mišić, B., Goñi, J., Betzel, R. F., Sporns, O., & McIntosh, A. R. (2014). A Network Convergence Zone in the Hippocampus. *PLOS Computational Biology, 10*(12), e1003982. doi:10.1371/journal.pcbi.1003982
Modinos, G., Tseng, H.-H., Falkenberg, I., Samson, C., McGuire, P., & Allen, P. (2015). Neural correlates of aberrant emotional salience predict psychotic symptoms and global functioning in high-risk and first-episode psychosis. *Social Cognitive and Affective Neuroscience, 10*(10), 1429-1436. doi:10.1093/scan/nsv035
Molitor, R. J., Sherrill, K. R., Morton, N. W., Miller, A. A., & Preston, A. R. (2021). Memory Reactivation during Learning Simultaneously Promotes Dentate Gyrus/CA(2,3) Pattern Differentiation and CA(1) Memory Integration. *J Neurosci, 41*(4), 726-738. doi:10.1523/jneurosci.0394-20.2020
Mørch-Johnsen, L., Agartz, I., & Jensen, J. (2017). The Neural Correlates of Negative Symptoms in Schizophrenia: Examples From MRI Literature. *Clinical EEG and Neuroscience, 49*(1), 12-17. doi:10.1177/1550059417746214
Morosini, P. L., Magliano, L., Brambilla, L., Ugolini, S., & Pioli, R. (2000). Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social funtioning. *Acta Psychiatrica Scandinavica, 101*(4), 323-329. doi:https://doi.org/10.1034/j.1600-0447.2000.101004323.x
Mucci, A., Dima, D., Soricelli, A., Volpe, U., Bucci, P., Frangou, S., . . . Maj, M. (2015). Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. *Psychological Medicine, 45*(8), 1765-1778. doi:10.1017/S0033291714002943
Mucci, A., Vignapiano, A., Bitter, I., Austin, S. F., Delouche, C., Dollfus, S., . . . Galderisi, S. (2019). A large European, multicenter, multinational validation study of the Brief

Negative Symptom Scale. *European Neuropsychopharmacology, 29*(8), 947-959. doi:https://doi.org/10.1016/j.euroneuro.2019.05.006

Niznikiewicz, M. A., Kubicki, M., & Shenton, M. E. (2003). Recent structural and functional imaging findings in schizophrenia. *Current Opinion in Psychiatry, 16*(2). Retrieved from https://journals.lww.com/co-psychiatry/Fulltext/2003/03000/Recent_structural_and_functional_imaging_findings.2.aspx

Nolin, M., Malla, A., Tibbo, P., Norman, R., & Abdel-Baki, A. (2016). Early intervention for psychosis in Canada: what is the state of affairs? *The Canadian Journal of Psychiatry, 61*(3), 186-194.

Norman, R. M. G., Manchanda, R., Malla, A. K., Windell, D., Harricharan, R., & Northcott, S. (2011). Symptom and functional outcomes for a 5year early intervention program for psychoses. *Schizophrenia Research, 129*(2), 111-115. doi:https://doi.org/10.1016/j.schres.2011.04.006

Ogawa, S., Lee, T.-M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *proceedings of the National Academy of Sciences, 87*(24), 9868-9872.

Passingham, R. E., Stephan, K. E., & Kötter, R. (2002). The anatomical basis of functional localization in the cortex. *Nature reviews neuroscience, 3*(8), 606-616. doi:10.1038/nrn893

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., & Mechelli, A. (2011). Dysconnectivity in schizophrenia: Where are we now? *Neuroscience & Biobehavioral Reviews, 35*(5), 1110-1124. doi:https://doi.org/10.1016/j.neubiorev.2010.11.004

Public Health Agency of Canada. (2019). *Schizophrenia in Canada*. Retrieved from https://www.canada.ca/en/public-health/services/publications/diseases-conditions/schizophrenia-canada.html

Raucher-Chéné, D., Bodnar, M., Lavigne, K. M., Malla, A., Joober, R., & Lepage, M. (2022). Dynamic Interplay Between Insight and Persistent Negative Symptoms in First Episode of Psychosis: A Longitudinal Study. *Schizophrenia Bulletin, 48*(1), 211-219. doi:10.1093/schbul/sbab079

Reddy, I. R., Ukrani, J., Indla, V., & Ukrani, V. (2018). Creativity and psychopathology: Two sides of the same coin? *Indian journal of psychiatry, 60*(2), 168-174. doi:10.4103/psychiatry.IndianJPsychiatry_129_18

Ren, J., Huang, F., Zhou, Y., Zhuang, L., Xu, J., Gao, C., . . . Luo, J. (2020). The function of the hippocampus and middle temporal gyrus in forming new associations and concepts during the processing of novelty and usefulness features in creative designs. *Neuroimage, 214*, 116751. doi:https://doi.org/10.1016/j.neuroimage.2020.116751

Rubinov, M., & Bullmore, E. (2013). Schizophrenia and abnormal brain network hubs. *Dialogues in clinical neuroscience, 15*(3), 339-349. doi:10.31887/DCNS.2013.15.3/mrubinov

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage, 52*(3), 1059-1069.

Rybarczyk, B. (2011). Social and occupational functioning assessment scale (SOFAS). *LXIII, encyclopedia of clinical neuropsychology, 1*, 2313.

Sadeghi, D., Shoeibi, A., Ghassemi, N., Moridian, P., Khadem, A., Alizadehsani, R., . . . Nahavandi, S. (2021). An overview on artificial intelligence techniques for diagnosis of

schizophrenia based on magnetic resonance imaging modalities: Methods, challenges, and future works. *arXiv preprint arXiv:2103.03081*.

Samara, M. T., Engel, R. R., Millier, A., Kandenwein, J., Toumi, M., & Leucht, S. (2014). Equipercentile linking of scales measuring functioning and symptoms: Examining the GAF, SOFAS, CGI-S, and PANSS. *European Neuropsychopharmacology, 24*(11), 1767-1772. doi:https://doi.org/10.1016/j.euroneuro.2014.08.009

Sauvé, G., Brodeur, M. B., Shah, J. L., & Lepage, M. (2019). The Prevalence of Negative Symptoms Across the Stages of the Psychosis Continuum. *Harvard Review of Psychiatry, 27*(1). Retrieved from https://journals.lww.com/hrpjournal/Fulltext/2019/01000/The_Prevalence_of_Negative_Symptoms_Across_the.3.aspx

Schneider, F., Habel, U., Reske, M., Kellermann, T., Stöcker, T., Shah, N. J., . . . Schlösser, R. (2007). Neural correlates of working memory dysfunction in first-episode schizophrenia patients: an fMRI multi-center study. *Schizophrenia Research, 89*(1-3), 198-210.

Schoemann, A. M., Boulton, A. J., & Short, S. D. (2017). Determining Power and Sample Size for Simple and Complex Mediation Models. *Social Psychological and Personality Science, 8*(4), 379-386. doi:10.1177/1948550617715068

Schultz, C. C., Fusar-Poli, P., Wagner, G., Koch, K., Schachtzabel, C., Gruber, O., . . . Schlösser, R. G. M. (2012). Multimodal functional and structural imaging investigations in psychosis research. *European Archives of Psychiatry and Clinical Neuroscience, 262*(2), 97-106. doi:10.1007/s00406-012-0360-5

Shafiei, G., Markello, R. D., Makowski, C., Talpalaru, A., Kirschner, M., Devenyi, G. A., . . . Lepage, M. (2020). Spatial patterning of tissue volume loss in schizophrenia reflects brain network architecture. *Biological Psychiatry, 87*(8), 727-735.

Shepherd, S., Depp, C. A., Harris, G., Halpain, M., Palinkas, L. A., & Jeste, D. V. (2012). Perspectives on Schizophrenia Over the Lifespan: A Qualitative Study. *Schizophrenia Bulletin, 38*(2), 295-303. doi:10.1093/schbul/sbq075

Strauss, G. P., & Gold, J. M. (2016). A psychometric comparison of the clinical assessment interview for negative symptoms and the brief negative symptom scale. *Schizophrenia Bulletin, 42*(6), 1384-1394.

Strauss, G. P., Nuñez, A., Ahmed, A. O., Barchard, K. A., Granholm, E., Kirkpatrick, B., . . . Allen, D. N. (2018). The Latent Structure of Negative Symptoms in Schizophrenia. *JAMA Psychiatry, 75*(12), 1271-1279. doi:10.1001/jamapsychiatry.2018.2475

Strauss, G. P., Wilbur, R. C., Warren, K. R., August, S. M., & Gold, J. M. (2011). Anticipatory vs. consummatory pleasure: what is the nature of hedonic deficits in schizophrenia? *Psychiatry research, 187*(1-2), 36-41. doi:10.1016/j.psychres.2011.01.012

Sumiyoshi, C., & Sumiyoshi, T. (2015). Functional Outcome in Patients With Schizophrenia: The Concept and Measurement. *Activitas Nervosa Superior, 57*(1), 1-11. doi:10.1007/BF03379619

Suzuki, T. (2011). Which rating scales are regarded as 'the standard' in clinical trials for schizophrenia? A critical review. *Psychopharmacology bulletin, 44*(1), 18-31. Retrieved from https://pubmed.ncbi.nlm.nih.gov/22506437
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5044554/

Tsang, A., Bucci, S., Branitsky, A., Kaptan, S., Rafiq, S., Wong, S., . . . Varese, F. (2021). The relationship between appraisals of voices (auditory verbal hallucinations) and distress in

voice-hearers with schizophrenia-spectrum diagnoses: A meta-analytic review. *Schizophrenia Research, 230*, 38-47. doi:https://doi.org/10.1016/j.schres.2021.02.013
Uddin, L. Q., Yeo, B. T. T., & Spreng, R. N. (2019). Towards a Universal Taxonomy of Macro-scale Functional Human Brain Networks. *Brain Topography, 32*(6), 926-942. doi:10.1007/s10548-019-00744-6
Van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology, 20*(8), 519-534. doi:https://doi.org/10.1016/j.euroneuro.2010.03.008
Van den Heuvel, M. P., Sporns, O., Collin, G., Scheewe, T., Mandl, R. C. W., Cahn, W., . . . Kahn, R. S. (2013). Abnormal Rich Club Organization and Functional Brain Dynamics in Schizophrenia. *JAMA Psychiatry, 70*(8), 783-792. doi:10.1001/jamapsychiatry.2013.1328
Van Erp, T. G. M., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., . . . for the, E. S. W. G. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry, 21*(4), 547-553. doi:10.1038/mp.2015.63
Van Erp, T. G. M., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., . . . Hashimoto, R. (2018). Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biological Psychiatry, 84*(9), 644-654.
Verdolini, N., & Vieta, E. (2021). Resilience, prevention and positive psychiatry. In (Vol. 143, pp. 281-283): Wiley Online Library.
Vesterager, L., Christensen, T. Ø., Olsen, B. B., Krarup, G., Melau, M., Forchhammer, H. B., & Nordentoft, M. (2012). Cognitive and clinical predictors of functional capacity in patients with first episode schizophrenia. *Schizophrenia Research, 141*(2), 251-256. doi:https://doi.org/10.1016/j.schres.2012.08.023
Vieira, S., Gong, Q., Scarpazza, C., Lui, S., Huang, X., Crespo-Facorro, B., . . . Mechelli, A. (2021). Neuroanatomical abnormalities in first-episode psychosis across independent samples: a multi-centre mega-analysis. *Psychological Medicine, 51*(2), 340-350. doi:10.1017/S0033291719003568
White, T., Cullen, K., Rohrer, L. M., Karatekin, C., Luciana, M., Schmidt, M., . . . Lim, K. O. (2008). Limbic Structures and Networks in Children and Adolescents With Schizophrenia. *Schizophrenia Bulletin, 34*(1), 18-29. doi:10.1093/schbul/sbm110
Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connectivity, 2*(3), 125-141. doi:10.1089/brain.2012.0073
Wilcoxon, F. (1945). Some uses of statistics in plant pathology. *Biometrics Bulletin, 1*(4), 41-45.
Yeo, T. B., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., . . . Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of neurophysiology*.
Zhao, C., Zhu, J., Liu, X., Pu, C., Lai, Y., Chen, L., . . . Hong, N. (2018). Structural and functional brain abnormalities in schizophrenia: A cross-sectional study at different stages of the disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 83*, 27-32. doi:https://doi.org/10.1016/j.pnpbp.2017.12.017
Zhou, M., Zhuo, L., Ji, R., Gao, Y., Yao, H., Feng, R., . . . Huang, X. (2022). Alterations in functional network centrality in first-episode drug-naïve adolescent-onset schizophrenia. *Brain Imaging and Behavior, 16*(1), 316-323. doi:10.1007/s11682-021-00505-9

ANNEX: PUBLISHED META-ANALYSIS IN NEUROSCIENCES AND BIOBEHAVIORAL REVIEWS (JANUARY 2022) WITH STUDENT AS FIRST-AUHTOR

Neuroscience and Biobehavioral Reviews 132 (2022) 37–49

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Structural brain correlates of cognitive function in schizophrenia: A meta-analysis

Marianne Khalil [a,b], Philippine Hollander [b,c], Delphine Raucher-Chéné [a,b,d,e], Martin Lepage [a,b], Katie M. Lavigne [a,b,f,*]

[a] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[b] Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada
[c] Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands
[d] Department of Psychiatry, University Hospital of Reims, EPSM Marne, Reims, France
[e] Cognition, Health, and Society Laboratory (EA 6291), University of Reims, Champagne-Ardenne, Reims, France
[f] Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

ARTICLE INFO

Keywords:
Brain networks
Volume
Cognitive domains
Speed of processing
Attention
Memory
Executive function
Social cognition

ABSTRACT

Schizophrenia is characterized by cognitive impairments and widespread structural brain abnormalities. Brain structure-cognition associations have been extensively studied in schizophrenia, typically involving individual cognitive domains or brain regions of interest. Findings in overlapping and diffuse brain regions may point to structural alterations in large-scale brain networks. We performed a systematic review and meta-analysis examining whether brain structure-cognition associations can be explained in terms of biologically meaningful brain networks. Of 7,261 screened articles, 88 were included in a series of meta-analyses assessing publication bias, heterogeneity, and study quality. Significant associations were found between overall brain structure and eight MATRICS-inspired cognitive domains. Brain structure mapped onto the seven Yeo functionally defined networks and extraneous structures (amygdala, hippocampus, and cerebellum) typically showed associations with conceptually related cognitive domains, with higher-level domains (e.g., executive function, social cognition) associated with more networks. These findings synthesize the extensive literature on brain structure and cognition in schizophrenia from a contemporary network neuroscience perspective and suggest that brain structure-cognition associations in schizophrenia may follow functional network architecture.

1. Introduction

Schizophrenia is a debilitating psychiatric disorder affecting approximately 20 million individuals worldwide (James et al., 2018). Schizophrenia is primarily characterized by positive (e.g., hallucinations, delusions) and negative (e.g., reduced motivation, flattened affect) symptoms; however, another core feature of schizophrenia involves impaired cognitive abilities (Kahn and Keefe, 2013; Kahn et al., 2015). Cognitive impairments are observed in the majority of individuals diagnosed with schizophrenia and are present across a wide range of domains (attention, memory, executive function; Heinrichs and Zakzanis, 1998; Schaefer et al., 2013). To characterize the cognitive domains impacted by schizophrenia and encourage novel treatments, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) categorized cognitive measures into seven neurocognitive domains: speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition (Marder, 2006; Nuechterlein et al., 2008). Cognitive impairments emerge early in the illness, typically preceding and even outlasting many of the clinical

Abbreviations: AC_1, Gwet's agreement coefficient; ATT, attention and vigilance; BANKSTS, banks of the superior temporal sulcus; CI, confidence interval; DAN, dorsal attentional network; DMN, default mode network; FDR, false-discovery rate; FPN, frontoparietal network; IFG, inferior frontal gyrus; LIM, limbic network; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MRI, magnetic resonance imaging; R&EF, reasoning and executive function; ROI, region of interest; SC, social cognition; SP, speed of processing; VAN, ventral attentional network; VF, verbal fluency; VIS, visual network; VisM, visual learning and memory; VM, verbal learning and memory; WM, working memory.

* Corresponding author at: F1128.1, 6875 boulevard Lasalle, Frank B. Common Pavilion, Douglas Mental Health University Institute, Montreal, QC, H4H 1R3, Canada.
E-mail address: katie.lavigne@mcgill.ca (K.M. Lavigne).

https://doi.org/10.1016/j.neubiorev.2021.11.034
Received 14 April 2021; Received in revised form 18 November 2021; Accepted 21 November 2021
Available online 23 November 2021

symptoms since cognitive deficits are often not remediated with pharmacological treatment (Kitchen et al., 2012; Lepage et al., 2014). In high-risk groups, cognitive deficits also predict the onset of psychosis – independently of other comorbidities – making it an important risk factor for schizophrenia (Seidman et al., 2016). Cognitive performance has also been found to be a strong predictor of poor functional outcomes in schizophrenia compared to other clinical symptoms (Lepage et al., 2014). This persistence of cognitive impairments in schizophrenia, from the prodrome to first episode to enduring schizophrenia, may be reflected in structural brain alterations.

Structural imaging studies of patients with schizophrenia have consistently shown a widespread decrease in cortical gray matter volume compared to healthy controls, especially in frontal and medial temporal areas (Shenton et al., 2001; van Erp et al., 2018) as well as in subcortical structures including the hippocampus and amygdala (van Erp et al., 2016). Research focusing on surface area and cortical thickness, which together constitute brain volume, has found extensive cortical thinning and reduced surface area across the cortical mantle in schizophrenia (van Erp et al., 2018). Given the pervasive brain and cognitive alterations in schizophrenia, a large literature has examined whether structural brain abnormalities (e.g., decreased volume, cortical thinning, reduced surface area) are associated with cognitive deficits in schizophrenia, culminating in several reviews and targeted meta-analyses (Antoniades et al., 2018; Antonova et al., 2004; Crespo-Facorro et al., 2007; Fujiwara et al., 2015; Gur et al., 1997; Kelly et al., 2019; Ventura et al., 2009).

Briefly, deficits in speed of processing have been correlated with a reduced temporal lobe volume and increased ventricular size (Antonova et al., 2004). Attentional impairments were correlated with structural alterations (e.g., decreased volume and grey matter density, cortical thinning) within the frontal and temporal lobes (Kelly et al., 2019) as well as with widespread reduced volume of subcortical regions (Antonova et al., 2004). Decreased working memory was correlated with reduced frontal and temporal lobe volumes and cortical thickness (Antoniades et al., 2018; Crespo-Facorro et al., 2007) while verbal learning and memory deficits were correlated with hippocampal volume loss (Antonova et al., 2004; Kelly et al., 2019). Impaired visual learning and memory correlated with hippocampal volume loss and with lower frontal and primary visual occipital volumes (Antonova et al., 2004; Kelly et al., 2019). Deficits in reasoning and problem solving, including higher-order executive functions, were also associated with a reduced frontal lobe volume, more specifically the dorsolateral prefrontal cortex (Antonova et al., 2004; Gur et al., 1997). Finally, impaired social cognition was linked to several structural deficits in the amygdala, prefrontal cortex, temporal and parietal lobes including reduced grey-matter and white-matter volumes (Fujiwara et al., 2015). Notably, while these reviews and meta-analyses show clear associations between brain structure and cognition in schizophrenia, brain structure-cognition findings from individual studies are equivocal.

Network neuroscience may provide a framework within which to better understand these complex findings. Previous selective reviews highlight brain structure-cognition associations within overlapping brain regions in schizophrenia, which may point to fundamental structural alterations within large-scale brain networks. It is becoming increasingly recognized that symptoms of schizophrenia are likely subtended by disruptions of integrated networks of brain regions rather than to damage in specific areas (Glover et al., 2012; Pettersson-Yeo et al., 2011). The extensive morphometric changes in schizophrenia, combined with the overlap of several regions associated with complex cognitive functions, reinforces the need to shift from a regional to network perspective in structural neuroimaging studies (Bassett and Sporns, 2017; Park and Friston, 2013; Uddin et al., 2019).

One well-known functional network parcellation is that of Yeo and colleagues (2011), who identified 7 and 17 cortical brain networks from resting-state functional connectivity. The canonical 7 networks were named based on their function as identified in the literature and include: the default mode network (DMN) active during rest as the default setting of the brain; the dorsal attention network (DAN) for externally directed attention to tasks; the frontoparietal control network (FPN) for goal-directed executive control; the limbic network (LIM) processing emotions and affect; the somatic network (SOM) responsible for motor movements and somatic sensations; the ventral attention network (VAN) for attention to salient stimuli and involuntary actions; and visual network (VIS) responsible for vision and direction in space. Connectivity-based brain parcellations such as this one are typically derived from functional or diffusion-weighted magnetic resonance imaging (MRI; Eickhoff et al., 2018) and further investigation is needed to determine whether anatomically-derived networks (e.g., structural covariance; Evans, 2013) follow the same topography as functional networks. However, examination of structural alterations (e.g., volume reductions) within functional networks, such as those by Yeo and colleagues (Yeo et al., 2011), can help characterize complex structural abnormalities in schizophrenia (Shafiei et al., 2020) and associations between brain structure and symptoms in schizophrenia (Kirschner et al., 2020). Notably, Kirschner et al. (2020) observed associations between the default mode and visual networks with a domain comprising cognitive deficits and negative symptoms, two stable hallmarks of schizophrenia, findings which shed light on potential structure-function associations in schizophrenia and its relation to clinical dimensions of the disease. Thus, reframing the structure-cognition literature in schizophrenia from the perspective of functional brain architecture may shed light on the complexity of brain structure-cognition associations in schizophrenia.

1.1. Rationale and objectives

Despite extensive research on morphological markers of cognitive deficits in schizophrenia, a comprehensive quantitative synthesis of the literature has yet to be performed. Thus, we systematically reviewed the structural MRI literature to date on brain structure-cognition associations in schizophrenia and performed a series of meta-analyses to synthesize the literature on associations between brain structure (e.g., volume, cortical thickness, surface area) and MATRICS-inspired cognitive domains (speed of processing, attention/vigilance, working memory, verbal and visual learning and memory, reasoning and executive function, social cognition, and verbal fluency) in schizophrenia. Whole-brain meta-analyses were first conducted to confirm associations between a given domain and overall brain structure in schizophrenia as well as assess risk of bias and study quality. Then, we examined specific network-cognitive domain associations by mapping structural findings onto functional network topography using the seven networks defined by Yeo et al. (2011) to investigate network-cognition associations. We expected that situating brain structure-cognition associations within functional network topography would provide a better understanding of the complex interrelations between cognitive domains and brain structure reported in the literature.

2. Methods

2.1. Protocol and registration

This study protocol was pre-registered on PROSPERO: https://www.crd.york.ac.uk/prospero/ (CRD42020206152). The PRISMA guidelines for systematic reviews and meta-analyses were followed (Moher et al., 2009). The PRISMA checklist for the current study is provided in the supplementary material.

2.2. Information sources and search strategy

A comprehensive literature search was conducted using OVID (MEDLINE, PsycInfo, Health and Psychosocial Instruments, and EMBASE) and EBSCO (CINAHL) databases on August 3rd, 2020. The

following keywords were used: (schizophreni* OR psychosis) AND (cogniti* OR attention OR vigilance OR speed of processing OR processing speed OR reasoning OR problem solving OR executive function OR verbal memory OR verbal learning OR visual memory OR visual learning OR working memory) AND (brain structure* OR morphometr* OR volume OR cortical thickness OR surface area). Reference lists of selected articles were also examined for additional studies. Evidence sources were limited to peer-reviewed articles, and we excluded book chapters, conference abstracts, and poster presentations manually.

2.3. Eligibility criteria

Retrieved articles were screened according to the following inclusion criteria: (a) peer-reviewed article; (b) reported on individuals with a diagnosis of schizophrenia-spectrum disorder (schizophrenia, schizoaffective, and schizophreniform disorders), and (c) included direct associations between cognition and brain structure (e.g., volume, thickness, surface area) using structural magnetic resonance imaging (T1-weighted or T2-weighted MRI). Both French and English peer-reviewed articles were included. Studies including only individuals presenting a diagnosis of a non-primary psychotic disorder (e.g., bipolar disorder with psychosis, delusional disorder, major depression with psychotic features, Alzheimer's/dementia with psychosis), or child-onset schizophrenia, first-episode psychosis, or who were at-risk for developing psychosis were excluded. Studies reporting combined results of schizophrenia-spectrum patients and healthy controls were excluded but those combining schizophrenia and first-episode psychosis, or a non-primary psychotic disorder were included if the proportion of schizophrenia-spectrum patients was larger than half the sample. We also excluded studies that grouped several cognitive tests, morphometric measures, or multiple neuroimaging modalities in their assessment of structure-cognition associations as they could not be separated for our meta-analyses. Finally, authors of studies that did not report sufficient data for the meta-analysis were contacted to obtain additional information.

2.4. Selection of sources of evidence

Articles retrieved from OVID and EBSCO were combined in EndNote software (The EndNote Team, 2013) and duplicates were removed automatically by comparing the Author, Year, Title, and Journal fields. Duplicates based on smaller combinations of these fields were then checked manually. The remaining unique articles were randomly ordered and assigned to one of three independent raters (MK, KML, VM) to assess titles and abstracts based on the article selection criteria. All three raters screened the same 200 articles (100 at the beginning and 100 at the end of the selection process) to assess inter- and intra- rater reliability (Belur et al., 2018). The ratings of each set of 100 articles were compared between raters and statistical agreement between was computed with the Gwet agreement coefficient (AC_1). AC_1 was used to control for the Kappa paradox, when low agreement between raters is due to highly similar raters (Gwet, 2008; Wongpakaran et al., 2013). Intra-rater reliability was assessed by computing the percentage of agreement between an article's final consensus rating and the rater's score (Belur et al., 2018). Discrepancies and questionable articles were resolved by a consensus between raters.

2.5. Data extraction

Full texts of the selected articles were retrieved, and data were extracted using a pre-developed form by two independent reviewers (MK, PH). Quality control of full extractions was done for approximately 45 % of articles by an independent reviewer (CL). Two additional independent reviewers (DRC, KML) reviewed the cognitive domain and network categorizations of all reported findings. The extracted information included demographic details (sample size, diagnosis, sex ratio, and age of patients and controls, if applicable), structural MRI metric (e.g., volume, cortical thickness, surface area), structural MRI brain coverage (e.g., vertex, regions of interest (ROIs), whole brain), cognitive measures (cognitive test, cognitive score), and the direct link between the structural and cognitive measures (analysis technique, the value of effect, statistic type and significance).

Cognitive tests were categorized into eight domains including the seven MATRICS domains (Nuechterlein et al., 2008): speed of processing (SP), attention and vigilance (ATT), working memory (WM), verbal learning and memory (VM), visual learning and memory (VisM), reasoning and problem solving, and social cognition (SC). Verbal fluency (VF) was added as an eighth domain, as its role within speed of processing has been questioned (Nuechterlein et al., 2004). Furthermore, the MATRICS domain reasoning and problem solving was renamed reasoning and executive functions (R&EF) to include tasks measuring executive functioning that were not typically part of the MATRICS categorization, as done previously (Lavigne et al., 2020; Van Rheenen and Rossell, 2014). We included all tests described as cognitive assessments in identified studies and categorized them by cognitive domain based on consensus in the field and intended use in the study (see Table S1). For example, SP included the trail-making test A and symbol coding tests, ATT was assessed with the Stroop test or Continuous Performance Tests, WM included digit or memory span tasks, VM included the California Verbal Learning Test and Hopkins Verbal Learning Test, VisM was assessed with facial and visual retention tasks, R&EF grouped trail-making test B and Wisconsin Card Sorting Test, SC had the Degraded Facial Affect Recognition Task as well as theory of mind assessments and VF included letter and category naming tests. Finally, for tasks in which a higher score indicated lower performance (e.g., Trail-making Test, Wisconsin Card Sorting Task perseverative errors), the sign of the correlation was reversed.

2.6. Quality assessment of individual studies

In order to assess the quality of included studies, we developed a rating system inspired by the newly implemented scales of quality assessment of arterial spin labeling functional MRI studies (Sukumar et al., 2020) based on recommendations in the field (Alsop et al., 2015). Thus, we extracted five parameters (segmentation/atlas, multiple comparison correction, covariates, nonsignificant results, and scanner strength) each of which were rated on a scale of 0–1 and then the total of the 5 ratings was used to assess article quality. We extracted the type of segmentation or brain atlas/coordinates used (e.g., ROI-based coordinates, manual, semi-automatic, automatic; 0 = not reported, 1 = reported) which is necessary to anatomically-define brain areas and ensure replicability. We also extracted whether the article included correction for multiple comparisons (0 = not reported, 1 = reported) which is important to control for the overall significance level in the case of multiple tests (Poldrack et al., 2017). When extracting covariates, if age and sex were controlled for, the article was rated 1 and if either one was controlled for, the article was rated 0.5. Controlling for age and sex as covariates is essential due to their well-established association with brain structure and cognition beyond disease-related factors (Gennatas et al., 2017). We also indicated if studies reported nonsignificant results (0 = not reported, 1 = reported) since this impacts publication bias (Müller et al., 2018). Finally, we extracted the scanner strength. If the scanner strength was larger than 1.5 T, the article was rated 1, otherwise, it was rated 0. All studies that had a total of 3 or more on the previous criteria were labeled high in quality while studies below 3 were labeled low in quality.

2.7. Meta-analysis

We used the Comprehensive Meta-Analysis (CMA) software (version 2.2.021, Biostat, Englewood, NJ) to perform our meta-analyses. We chose Fisher's Z to present our results since the primary outcome

involved correlations between brain regions and cognitive domains. Fisher's Z transformations were calculated for each study from the reported statistical effect (i.e., Pearson's correlation, Spearman's rho, t-tests or p-values) and sample size. Meta-analyses were conducted using a random effects model, which assumes that the true effect size of each of the studies varies and is not due to sampling variance only (Hall and Rosenthal, 2018). Additionally, the software weights studies based on their sample size which is important to control for effects driven by studies with a small number of patients that may be heterogenous.

We first performed eight overall meta-analyses of the correlations between each cognitive domain and all brain structure findings (refer to supplementary Fig. S1 for the meta-analyses schematic process). We assessed publication bias and heterogeneity of studies at this overall level. We then performed 10 subgroup analyses for each cognitive domain to further characterize these overall effects in terms of the seven Yeo et al. (2011) brain networks and three additional brain regions (i.e., hippocampus, amygdala, cerebellum) that emerged consistently in our systematic review. We controlled for multiple comparisons using the false discovery rate (FDR), a robust control for loss of power in studies with high throughput (Benjamini and Hochberg, 1995) for all of the ten subgroup analyses in each of the eight domains. We set the FDR to 0.05 which is the alpha used in the eight general meta-analyses.

2.7.1. Whole brain & cognitive domains

The overall meta-analyses on correlations between all reported structures and each of the cognitive domains included all the structural metrics (i.e., volume, cortical thickness, surface area). We aggregated all structures and morphometric measures associated in the literature for each of the eight cognitive domains and ran overall analyses to observe general trends and inform our follow-up network analyses.

2.7.1.1. Risk of bias across studies. We assessed risk of bias across studies for each of the eight overall meta-analyses. Publication bias, defined as the impact that results have on the publication of a study (Easterbrook et al., 1991), was assessed with two quantitative tests: Egger's asymmetry test and the fail-safe N of Rosenthal. Given the large number of studies in each of the eight meta-analyses (see Section 3.3), qualitative assessments (e.g., visual inspection of funnel plots) were not used. Egger's asymmetry test, a rank test, examines the significance of the correlation between effect sizes and their corresponding sampling variances and a significant result is likely evidence of publication bias (Egger et al., 1997). The fail-safe N of Rosenthal refers to the number of additional 'negative' studies that would be needed to increase the p value for a given meta-analysis to above 0.05 (Rosenthal, 1979). Usually, if the fail-safe N is larger than five times the number of studies included in the analysis plus ten then there is little evidence of publication bias (Fragkos et al., 2014).

We also assessed heterogeneity, the variation in outcomes between studies, with two quantitative tests: Cochran's Q and the I^2 Index. For Cochran's Q, a p-value less than 0.1 indicates heterogeneity (Cochran, 1950). Cochran's Q is a commonly used method but has low power when the number of studies is small and excessive power when the number of studies becomes large (Pereira et al., 2010). This posed a problem for our meta-analysis due to the variation in the number of studies for each domain. Thus, we supplemented our heterogeneity assessment with the I^2 statistic, which is not impacted by the number of studies in the meta-analysis (Pereira et al., 2010). The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance with general effect size cut-offs of 25 % (small), 50 % (medium) and 75 % (large; Higgins and Thompson, 2002).

2.7.1.2. Quality assessment. Following the overall meta-analyses, we also performed two subgroup analyses for each of the eight domains by filtering for the quality of the studies (low/high quality based on ratings described in Section 2.6). We then performed, using the CMA software, a z-test comparing the mean difference between the two subgroups to determine whether there was a significant difference between low- and high-quality studies.

2.8. Network-mapped subgroup analyses

We performed a series of subgroup analyses to study the specific associations between brain networks and cognition. To do so, we first classified brain regions from studies using the Desikan Killiany-Tourville atlas (Klein and Tourville, 2012) parcellation method, as done in Makowski et al. (2020), into the seven Yeo et al. (2011) networks: DMN, DAN, FPN, LIM, SOM, VAN and VIS. For other studies, we overlaid the Yeo atlas of the seven networks with the structural atlases reported (Broadman, AAL) to classify regions using MRIcron. If coordinates were provided, we were able to attribute a finding directly to a specific network. Consensus between authors was reached for the questionable classifications of brain regions. Studies which reported findings on larger brain areas (i.e., frontal lobe, temporal lobe) or unclassified structures (e.g., subcortical structures, white matter, ventricles, cerebellum, corpus callosum), were excluded from the network subgroup analyses. Given the importance of some of these regions in cognition and their prevalence in the identified literature (i.e., amygdala, hippocampus, cerebellum), these were assessed separately (see below) rather than excluded entirely. See Table S2 for a detailed description of the brain structures, and if applicable, their attributed network.

In CMA, we used the name of the network as a subgroup variable, laterality of the region as a differentiating variable and the name of the cognitive test as an outcome to perform seven sub-group analyses for each of the eight domains. To investigate the precise regions of the networks contributing to the correlation with cognition, we also ran more precise subgroup analyses with the name of the brain structures as a subgroup variable filtering for the brain structures with a significant network-domain association based on the previous subgroup analyses.

2.9. Other structures analyses

Specific structures (amygdala, hippocampus, overall cerebellum) were investigated with separate subgroup analyses as they have shown structural changes and cognitive correlations in the literature (Koshiyama et al., 2018). Other potentially relevant structures (i.e., thalamus, nucleus accumbens) were not included due to limited studies in the literature review. Finally, although the cerebellum has a common network parcellation to the Yeo et al. (2011) cerebral atlas (Buckner et al., 2011), studies generally reported overall correlations with the cerebellum, and we could not include it in the network analyses. Thus, we investigated these regions' correlations with cognition in three subgroup analyses for each of the eight domains.

3. Results

3.1. Study selection

The flowchart for article selection is displayed in Fig. 1. The database search identified 7,259 articles and two additional articles were identified by co-authors. After the removal of 4,931 duplicates, books, and conference abstracts, the remaining 2,330 titles and abstracts were randomly assigned to one of three raters. There were 199 articles flagged for full-text screening with the addition of 13 articles from reference lists. Although we included 115 articles in our systematic review (see Table S3), 27 were not included in the meta-analysis as they either represented review articles, did not report relevant values of effect and authors could not be reached, or used analysis techniques that were incompatible with our software (e.g., multivariate analysis). Thus, 88 original research articles were included in our meta-analyses. See Table S3 for a summary of studies included in the review and meta-analyses.

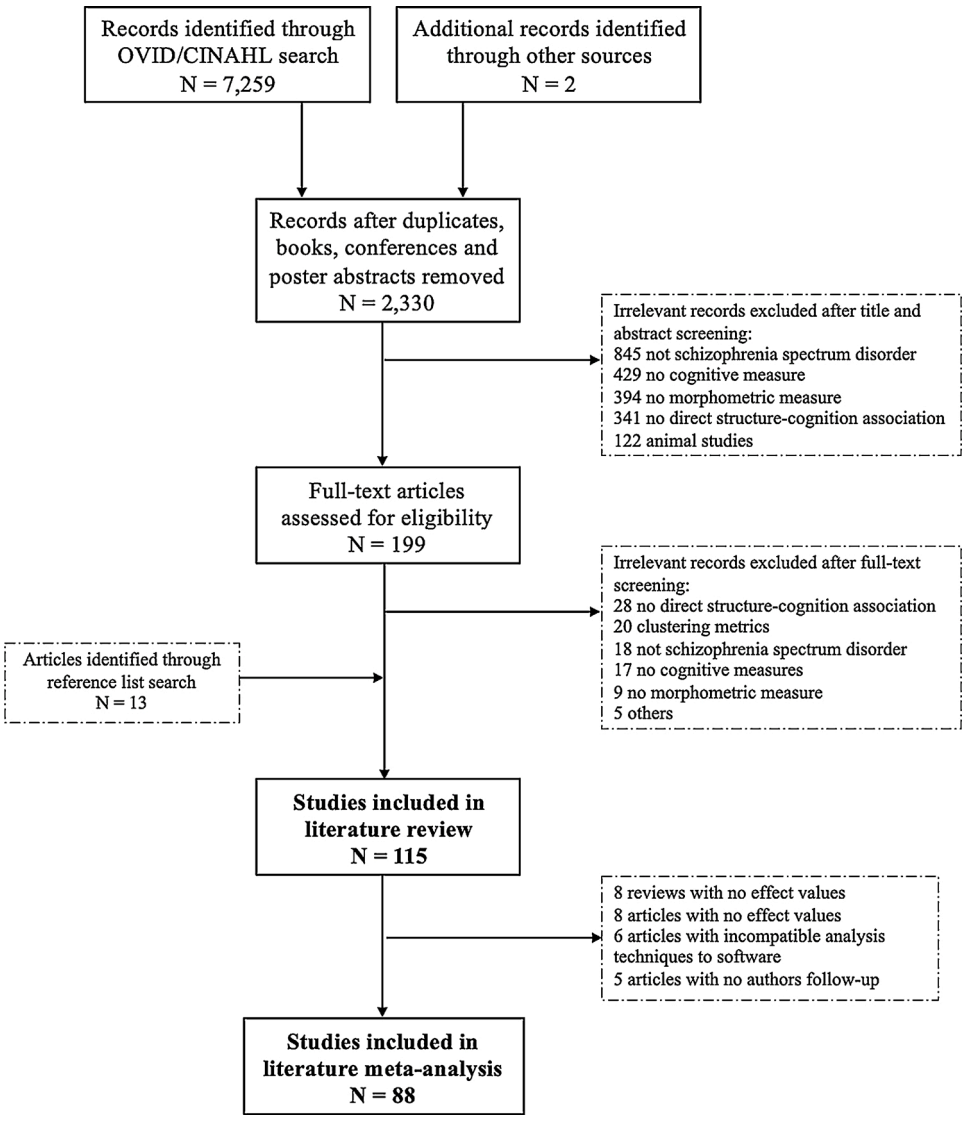


Fig. 1. Flow chart of the article selection process following PRISMA guidelines.

3.2. Raters' reliability

The results of AC_1 for the inter-rater reliability tests were high for both timepoints: IRR1 = 0.87 (SE = 0.03, 95 % CI = [0.80−0.93], $p < 0.001$) and IRR2 = 0.88 (SE = 0.03, 95 % CI = [0.82−0.95], $p < 0.001$). Additionally, the percentage of agreement between IRR1 (Rater 1: 92 %; Rater 2: 89 %; Rater 3: 92 %) and IRR2 was high (Rater 1: 95 %; Rater 2: 91 %; Rater 3: 95 %) and increased for all raters.

3.3. Whole brain & cognitive domains meta-analyses

We performed a meta-analysis for each of the eight cognitive domains to determine if they were correlated with overall brain structures, including all structural metrics. We found a significant summary Fisher's z for all domains, ranging from 0.087 (VF) to 0.669 (SC; see Fig. 2; Figs. S2-S11 for individual forest plots). The presence of a significant association between a given cognitive domain and overall brain structure allowed us to justify further investigations with network topography. To further explore the exceptionally strong association observed with SC relative to the other domains, we divided this domain into two sub-categories, emotion processing and theory of mind, based on the type of task reported in the article. Subgroup analyses, followed by a z-test to compare the difference of means, showed significant correlations between brain structures and both emotional processing (Fisher's z = 0.569, 95 % CI [0.258, 0.880]) and theory of mind (Fisher's z = 0.726, 95 % CI [0.610; 0.842]), with no significant differences between the two sub-domains ($p > 0.05$; see Fig. 2; Figs. S10-S11 for individual plots). Finally, when performing the overall meta-analyses, we found that for all cognitive domains, volume was the most reported metric for brain structures ranging between 78 % (SP) to 95 % (VM) of all included articles in the domains.

3.3.1. Risk of bias

We assessed publication bias with Egger's Asymmetry and Fail-Safe N of Rosenthal tests (see Table 1). Egger's Asymmetry test indicated potential publication bias ($p < 0.05$) for R&EF, SC, and VF; however, no evidence of bias was observed with the fail-safe N of Rosenthal, which was above the cut-off (five times the number of studies included in the analysis plus ten) for all cognitive domains. Furthermore, the Cochran's Q test for all domains had a p-value below 0.1 indicating heterogeneity between studies (Potvin, 2020). Similarly, the I^2 index signalled moderate to high heterogeneity between studies for all cognitive domains (I^2 range = 52.97 for SP to 96.80 for SC), except VF, which showed low-to-moderate heterogeneity (I^2 = 46.00).

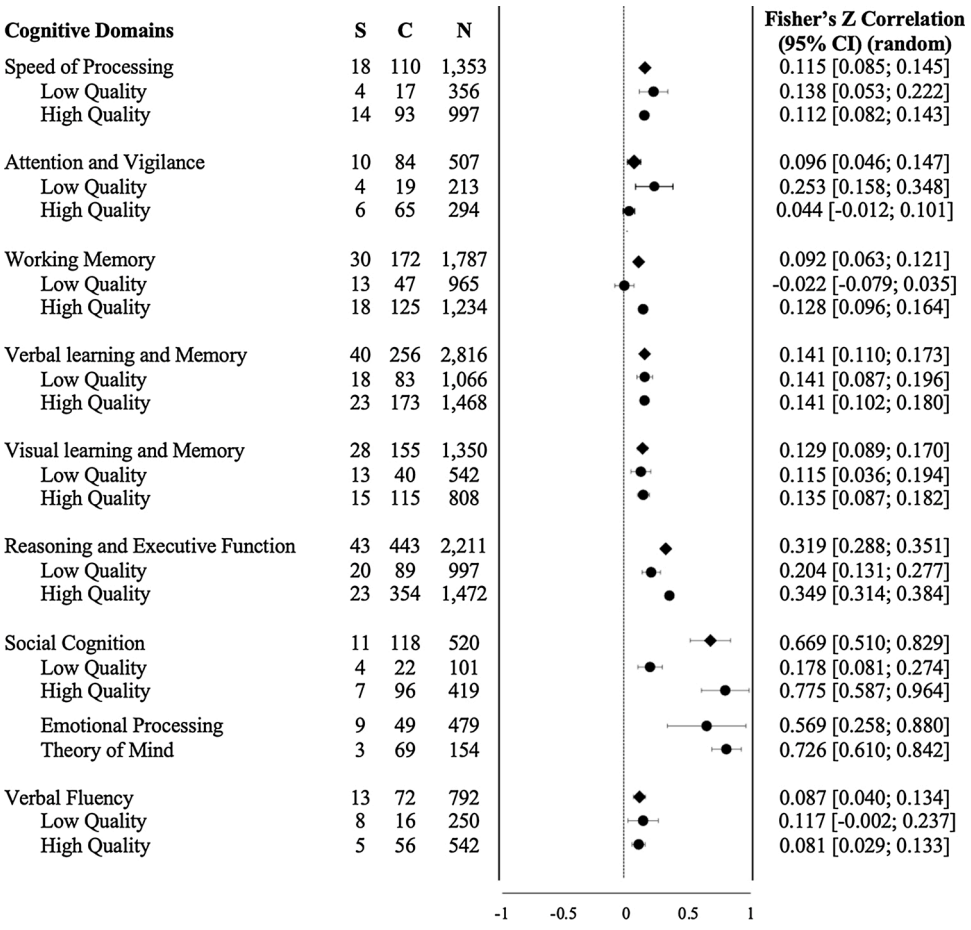


Fig. 2. Overall correlation between each cognitive domain and overall brain structures including all structural metrics. Subgroup analyses between low- and high-quality studies are also presented for each cognitive domain. The number of studies (S), correlations (C) and patients (N) are indicated for each of correlations. Error bars reflect 95% confidence intervals (CI).

Table 1
Results of publication bias tests and heterogeneity for each cognitive domain.

	Egger's (p-value)	Fail-Safe N	N cut-off *	Q (p-value)	I^2
SP	0.604 *(0.092)*	3,442	100	231.75 *(0.000)*	52.966
ATT	−0.506 *(0.219)*	655	60	209.57 *(0.000)*	60.395
WM	0.095 *(0.759)*	4,659	160	464.507 *(0.000)*	63.187
VM	0.202 *(0.463)*	4,016	210	733.52 *(0.000)*	65.236
VISM	0.469 *(0.134)*	4,014	150	406.896 *(0.000)*	62.153
R&EF	2.545 *(0.000)*	6,788	225	1671.59 *(0.000)*	73.558
SC	5.116 *(0.000)*	1,654	65	3655.88 *(0.000)*	96.800
VF	1.381 *(0.011)*	415	75	131.488 *(0.000)*	46.003

ATT: attention and vigilance; R&EF: reasoning and executive function; SC: social cognition; SP: speed of processing; VF: verbal fluency; VisM: visual learning and memory; VM: verbal learning and memory; WM: working memory.

* N cut-off = (number of studies × 5) + 10.

3.3.2. Quality assessment

The ratings of the included studies are displayed in the supplementary material (Table S4). Subgroup analyses followed by a test of the differences in means showed that, for ATT, low-quality studies were significantly more correlated with brain structures than those of high-quality (Z_{Diff} = -4.55, $p < 0.05$). For R&EF (Z_{Diff} = 4.62, $p < 0.05$), SC (Z_{Diff} = 2.71, $p < 0.05$) and WM (Z_{Diff} = 4.74, $p < 0.05$) high-quality studies showed a significantly larger correlation with brain structures than those of low quality. SP (Z_{Diff} = -0.581, $p > 0.70$), VF (Z_{Diff} = -0.443, $p > 0.05$), VisM (Z_{Diff} = 0.365, $p > 0.05$) and VM (Z_{Diff} = 0, $p > 0.05$) did not show evidence of significant difference between the correlations of low- and high-quality studies. The overall forest plot (Fig. 2) provides the Fisher's z correlation of each quality subgroup for comparison with the overall results of the overall meta-analyses for each domain.

3.4. Network subgroup analyses

Using brain network topography (Fig. 3), we found significant (connections displayed in color) and non-significant (connections displayed in greyscale) correlations between specific networks and cognitive domains in schizophrenia. Fig. 3 also highlights associations not investigated in the literature (no connections). Additionally, we were able to observe which brain structures within each network contributed to a significant correlation with a given cognitive domain (Fig. 4). The effect values of all the correlations between networks and domains as well as the brain structures and the domains are listed in Table S5 and visualized in the circle plots in Fig. S12.

SP was significantly associated with three networks: DMN (Fisher's z = 0.508, 95 % CI: [0.280; 0.737]), DAN (z = 0.576, [0.212; 0.940]) and FPN (z = 0.337, [0.106; 0.568]). For the DMN, the inferior temporal gyrus (z = 0.704, [0.346, 1.062]) was the brain structure mostly strongly correlated with the domain. For the DAN, it was the inferior frontal gyrus (IFG), pars opercularis (z = 0.576, [0.212, 0.940]) and for the FPN, it was the middle cingulate gyrus (z = 1.131, [0.658, 1.605]).

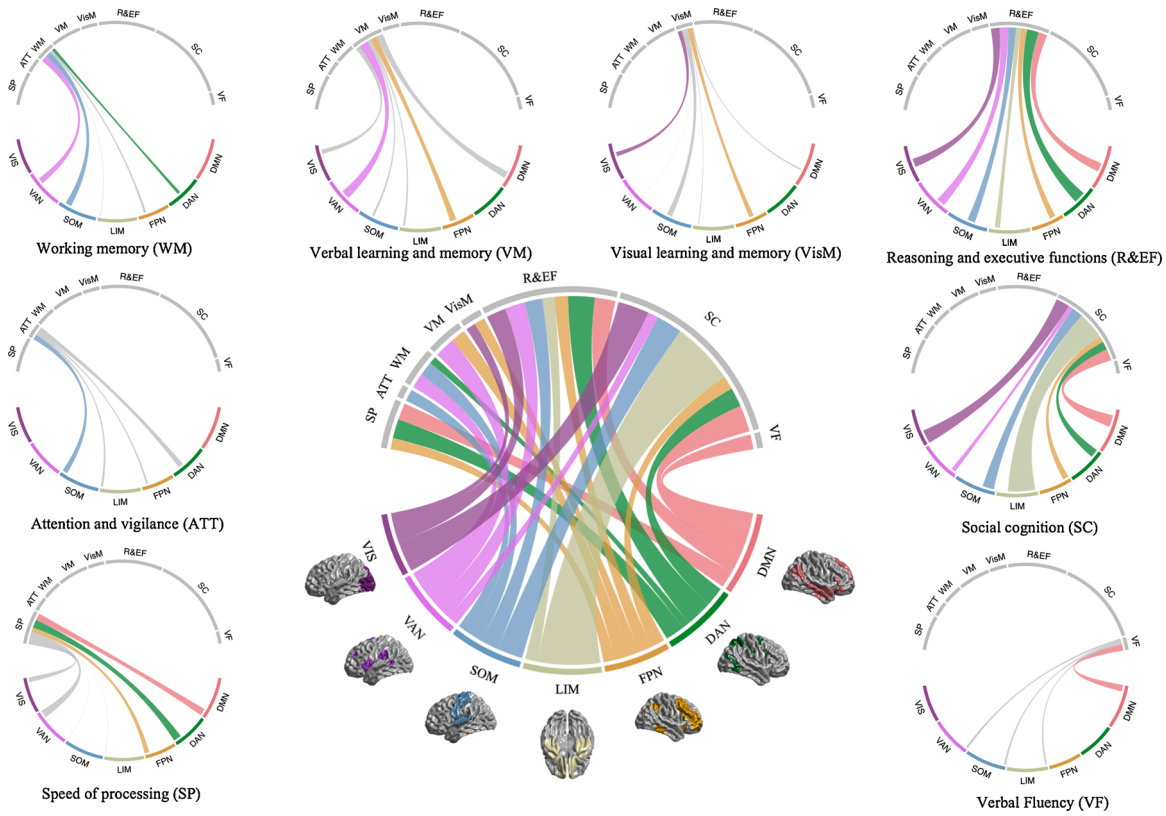


Fig. 3. Lower middle panel: circle plot of the significant FDR-corrected correlations between the seven brain networks and the eight cognitive domains. The thickness of the link is proportional to the correlation strength (Table S5). Surrounding panels (bottom left to bottom right): significant (in colour) and non-significant (grey) summary correlations for each cognitive domain. Unexplored associations are represented as absent links between a domain and network. DMN: default-model network, DAN: dorsal attention network, FPN: frontoparietal network, LIM: limbic network, SOM: somatosensory network, VAN: ventral attention network, VIS: visual network.

The **ATT** cognitive domain was found to be significantly correlated only with the SOM network ($z = 0.358$, [0.205; 0.511]) due to Heschl's gyrus which had the strongest significant correlation for this domain ($z = 0.551$, [0.351, 0.751]).

WM was associated significantly with three networks: DAN ($z = 0.221$, [0.048; 0.394]), SOM ($z = 0.436$, [0.276; 0.595]) and VAN ($z = 0.443$, [0.183; 0.702]). These network correlations were driven by the IFG pars opercularis ($z = 0.221$, [0.048, 0.394]) for the DAN, by the superior temporal gyrus ($z = 0.436$, [0.276, 0.595]) for the SOM network and by the superior frontal gyrus ($z = 0.572$, [0.202, 0.943]) for the VAN.

VM was correlated significantly with FPN ($z = 0.440$, [0.290; 0.590]) and VAN ($z = 0.622$, [0.253; 0.992]). It also correlated most strongly with the middle ($z = 0.576$, [0.182, 0.970]) and the superior ($z = 0.576$, [0.310, 0.843]) frontal gyri categorized in the FPN and VAN, respectively.

VisM was significantly associated with FPN ($z = 0.322$, [0.202; 0.443]) and VIS ($z = 0.291$, [0.072; 0.509]) networks. These network correlations were driven by IFG ($z = 0.465$, [0.286, 0.645]) for the FPN and by fusiform gyrus ($z = 0.291$, [0.072, 0.509]) for the VIS.

R&EF was significantly associated with all seven brain networks. These network correlations were driven by the anterior cingulate gyrus ($z = 0.694$, [0.556, 0.832]) for the DMN ($z = 0.620$, [0.542; 0.699]), by the IFG, pars opercularis ($z = 0.729$, [0.593, 0.864]) for the DAN ($z = 0.729$, [0.593; 0.864]), by the middle frontal gyrus ($z = 0.741$, [0.517, 0.966]) for the FPN ($z = 0.411$, [0.298; 0.523]), by the orbitofrontal cortex ($z = 0.423$, [0.269, 0.577]) for the LIM network ($z = 0.365$, [0.216; 0.513]), by the claustrum ($z = 0.769$, [0.351, 1.186]) for the SOM network ($z = 0.537$, [0.384; 0.690]), by the BANKSTS ($z = 0.775$, [0.569, 0.982]) for the VAN ($z = 0.604$, [0.511; 0.697]), and by the inferior occipital gyrus ($z = 0.803$, [0.385, 1.221]) for the VIS network ($z = 0.592$, [0.448; 0.734]).

The **SC** domain was also significantly associated with all the brain networks. These network correlations were driven by the posterior cingulate gyrus ($z = 1.722$, [0.134, 3.309]) for the DMN ($z = 0.804$, [0.356; 1.253]), the superior parietal lobule ($z = 0.929$, [0.467, 1.391]) for the DAN ($z = 0.929$, [0.467; 1.391]), the IFG, pars triangularis ($z = 0.640$, [0.056, 1.224]) for the FPN ($z = 0.411$, [0.237; 0.585]), the parahippocampal gyrus ($z = 2.215$, [0.585, 3.845]) for the LIM network ($z = 1.892$, [0.547; 3.236]), the superior temporal gyrus ($z = 0.963$, [0.637, 1.290]) for the SOM network ($z = 0.784$, [0.545; 1.024]), the middle cingulate gyrus ($z = 1.131$, [0.658, 1.605]) for the VAN ($z = 0.315$, [0.214; 0.415]), and the middle occipital gyrus ($z = 0.914$, [0.648, 1.181]) for the VIS network ($z = 0.914$, [0.648; 1.181]).

Finally, the **VF** domain was only correlated significantly with DMN ($z = 0.447$, [0.088; 0.806]) mostly driven by the strong association with the inferior temporal gyrus ($z = 0.678$, [0.172, 1.184]).

3.5. *Structures subgroup analyses*

Selected structures commonly emerging in the literature review included the amygdala, the cerebellum, and the hippocampus (Fig. 5). **SP** was significantly associated with the hippocampus ($z = 0.130$, [0.080, 0.180]) and the amygdala ($z = 0.204$, [0.141, 0.267]) while **ATT** was only significantly associated with the cerebellum ($z = 0.109$, [0.030, 0.188]). **WM** was found to be significantly correlated with all three structures (amygdala: $z = 0.136$, [0.081, 0.191]; cerebellum: $z = 0.800$, [0.141, 1.078]; hippocampus: $z = 0.159$, [0.115, 0.202]). **VM** was found to be associated significantly with the hippocampus ($z = 0.234$, [0.181, 0.287]) and **VisM** was found to be correlated

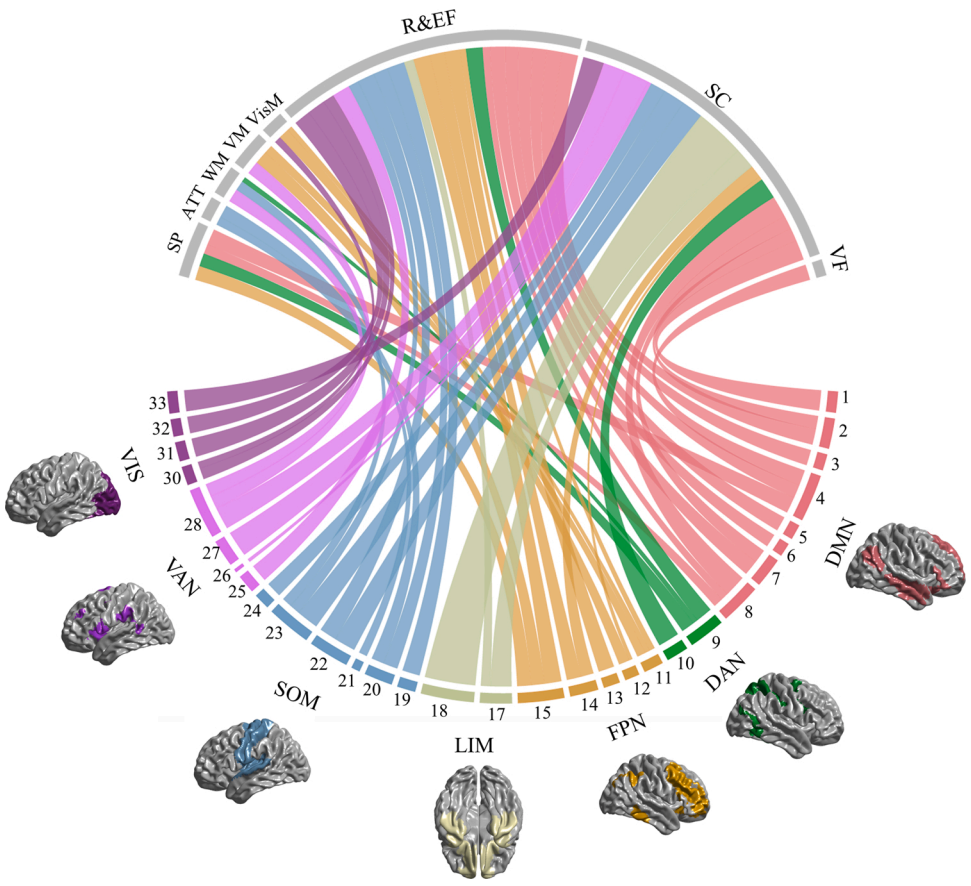


Fig. 4. Circle plot of the FDR significant correlations between the brain regions categorized in the seven brain networks and the eight cognitive domains. The thickness of the link is proportional to the correlation strength. The colors of the brain regions correspond to the respective network. The legend and the values of the effect are in Table S5. Non-significant correlations are shown in Fig. S12. ATT: attention and vigilance, DMN: default-model network, DAN: dorsal attention network, FPN: frontoparietal network, LIM: limbic network, R&EF: reasoning and executive function, SC: social cognition, SOM: somatosensory network, SP: speed of processing, VAN: ventral attention network, VF: verbal fluency, VIS: visual network, VisM: visual memory, VM: verbal memory, WM: working memory.
1: angular gyrus; 2: anterior cingulate gyrus; 3: IFG, pars orbitalis; 4: inferior parietal lobule; 5: inferior temporal gyrus; 6: lateral aspect; 7: middle temporal gyrus; 8: posterior cingulate gyrus; 9: precuneus; 10: temporal pole; 11: IFG, pars opercularis; 12: superior parietal lobule; 13: dorsolateral prefrontal cortex; 14: inferior frontal gyrus; 15: IFG, pars triangularis; 17: middle frontal gyrus; 18: entorhinal cortex; 19: gyrus rectus; 20: orbitofrontal cortex; 21: parahippocampal cortex; 22: claustrum; 23: Heschl's gyrus; 24: planum temporale; 25: precentral gyrus; 26: superior temporal gyrus; 27: supplementary motor area; 28: BANKSTS; 30: middle cingulate gyrus; 31: superior frontal gyrus; 32: temporoparietal junction; 33: calcarine cortex.

significantly with the cerebellum (z = 1.042, [0.816, 1.268]) and the hippocampus (z = 0.141, [0.063, 0.219]). The **R&EF** domain was significantly correlated with the hippocampus (z = 0.190, [0.111, 0.268]) and the amygdala (z = 0.169, [0.075, 0.263]). **SC** was significantly associated with the hippocampus (z = 1.263, [0.801, 1.725]) and the amygdala (z = 0.596, [0.351, 0.841]) . Finally, **VF** was significantly associated with the cerebellum (z = 0.201, [0.135, 0.267]).

4. Discussion

The aim of this study was to comprehensively synthesize the literature to date on associations between brain structure and cognition in schizophrenia as well as map structural findings correlated with cognition onto functional network topography using the seven networks defined by Yeo et al. (2011) to examine whether these could be better understood from a network perspective. We identified 115 articles investigating brain-cognition associations in schizophrenia, 88 of which were included in our meta-analyses. Overall, we found that all cognitive domains were generally associated with brain structure in schizophrenia. Brain network subgroup analyses provided deeper insight into these associations from a structure-function perspective and point to potential hub regions associated with distinct cognitive functions. Notably, we observed that higher-level cognitive processes (e.g., reasoning and executive function, social cognition) tend to be associated with a greater number of networks compared to other cognitive domains. We also identified specific network-cognition associations lacking in the literature that would be expected based on the network's functional characteristics. Thus, leveraging functional network topography allowed us to better characterize brain structure-cognition associations in schizophrenia, suggesting that brain structural correlates of cognition may follow network architecture.

4.1. Whole brain & cognitive domains meta-analyses

The overall set of meta-analyses yielded significant correlations between brain structure and all eight cognitive domains. The strongest overall brain-cognition associations were with SP, VM, VisM, R&EF and SC. These domains are also those with the most associated studies, which might reflect research trends in the field or more knowledge on structural regions associated with them than other domains. We detected publication bias for three domains (R&EF, SC, and VF). We thus acknowledge that this partiality in the literature might impact our results for these domains. Additionally, heterogeneity was present for all eight domains, which was expected due to the variability of methodologies across studies and our inclusion of multiple metrics and brain regions. Interestingly, VF was the only domain to show low heterogeneity, which might be partially due to this domain being primarily measured by two cognitive tests with little variation in scoring (letter and category fluency). The use of the random effects model in all meta-analyses to estimate the correlation between brain structure and cognitive domains was employed to remediate this and other potential sources of variation between studies (Lipsey and Wilson, 2001).

We also assessed the quality of the studies included in each of the eight meta-analyses and expected that the results of high-quality studies would differ significantly from those of low-quality. This was the case for ATT, R&EF, SC, and WM, suggesting that methodological differences relating to brain segmentation/atlas, multiple comparisons, covariates, nonsignificant results, and scanner strength have a strong impact on the overall correlation with brain structure for at least these domains. Surprisingly, larger effects were observed for low- relative to high-quality studies for ATT, which warrants further investigation. The remaining domains (SP, VM, VisM, and VF) did not show a significant difference between low- and high-quality studies, which could indicate that brain structure associations with these domains are less affected by these

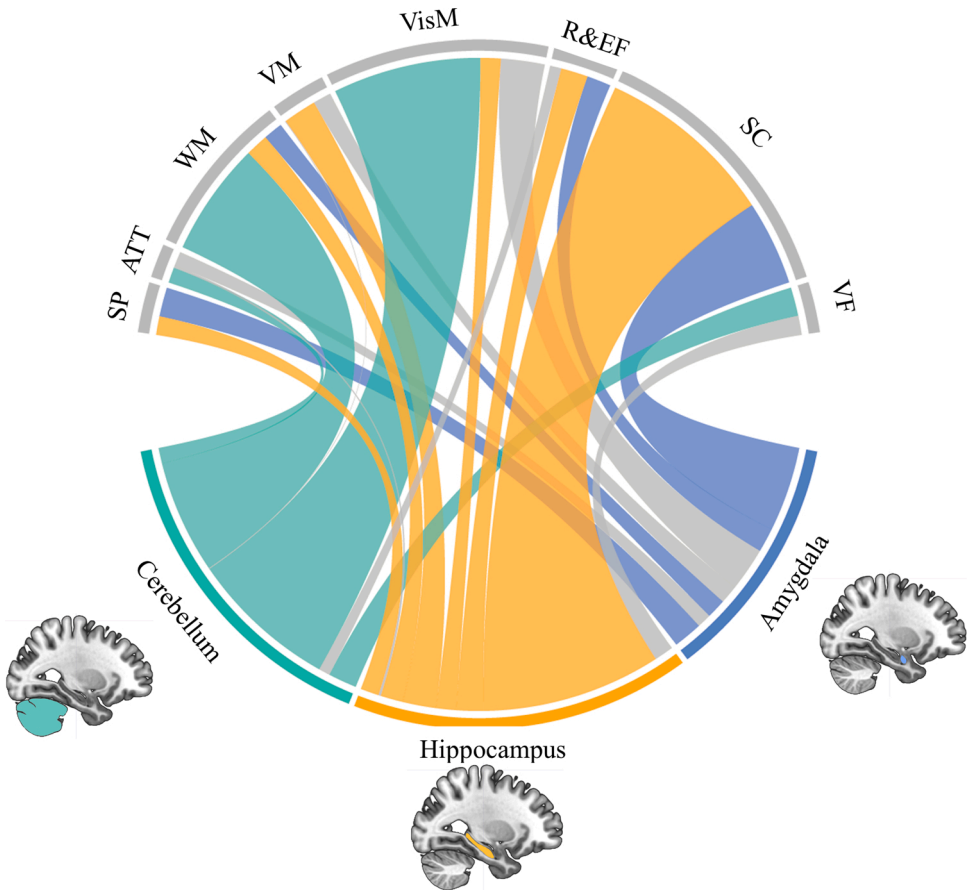


Fig. 5. Circle plot of the correlations between three structures not categorized in networks and the eight cognitive domains. The thickness of the link is proportional to the correlation strength (Table S6). The grey links are nonsignificant with FDR. ATT: attention and vigilance, R&EF: reasoning and executive function, SC: social cognition, SP: speed of processing, VF: verbal fluency, VisM: visual memory, VM: verbal memory, WM: working memory.

criteria, that there is a certain homogeneity in the way these domains have been assessed to date, or perhaps that the strength of the effects eclipses the confounding impact of the quality criteria. The subsequent network subgroup analyses aimed to address the additive effects of the overall analysis, which could hide more subtle correlations, and provide a targeted view of brain structure-cognition associations in schizophrenia.

4.2. Cognition and networks

Leveraging functional brain network architecture provided new insights concerning network-cognition associations in schizophrenia, revealing significant correlations between all cognitive domains and at least one brain network. Follow-up analyses allowed us to pinpoint within-network regions contributing most strongly to these network-cognition associations. Overall, we observed that associations between brain structure and cognition can be understood in terms of brain network architecture and key brain regions, which are interpreted by cognitive domain below.

4.2.1. Speed of processing

This domain was significantly associated with structural alterations in three networks: the DMN correlation was driven by inferior temporal gyrus, the DAN by IFG, pars opercularis, and the FPN by middle cingulate gyrus. These results are consistent with recent functional and effective connectivity findings indicating that digit symbol coding (the task most commonly employed within this domain) involves interactions between frontoparietal and inferior temporal/frontal systems involved in goal- and stimulus-directed behaviour (Silva et al., 2019). While the emergence of the DMN in the current study was unexpected, this network's effect was driven primarily by the inferior temporal gyrus, which has been designated a number-form area comprising a "symbolic number processing network" along with several other regions observed herein (e.g., inferior frontal gyrus; Yeo et al., 2017). The current findings suggest that these associations with speed of processing in healthy individuals may extend to schizophrenia and that structural alterations within these regions contribute to speed of processing deficits in schizophrenia. Concerning other structures, SP was significantly correlated with both the amygdala and the hippocampus involved in learning and memory (Andersen et al., 2006). This is in line with behavioral research indicating links between memory and processing speed in schizophrenia as well as the potential use of memory-related strategies to perform SP tasks (Brébion et al., 1998; Knowles et al., 2015). Finally, this domain did not show significant differences between low- and high- quality studies in the overall meta-analysis which could be due to high heterogeneity in neuroimaging methodology between studies. Previous meta-analyses pointed to the high variability in effect sizes of studies with coding tasks compared to other tasks of SP (Knowles et al., 2010).

4.2.2. Attention and vigilance

ATT was only significantly correlated with the SOM network, driven by Heschl's gyrus. The planum temporale, close to the temporo-parietal junction and part of the SOM network, was also significantly correlated with ATT supporting previous reviews' findings (Antonova et al., 2004; Lesh et al., 2011). This is likely due to several studies using auditory continuous performance tests to assess attention. We also expected DAN and VAN to significantly correlate with this domain, but surprisingly,

associations between ATT and regions within these attentional networks were rarely assessed in the literature. On one hand, the DAN showed a non-significant correlation, possibly due to the fact that only two associations with one specific brain region (IFG pars opercularis) were examined in the literature. On the other hand, studies did not report any correlations with brain regions categorized within the VAN. Thus, more research is necessary to determine whether structural associations with attention and vigilance in schizophrenia are limited to primary sensory regions or are also reflected in attention-related networks.

We also observed a significant correlation between this domain and the cerebellum, recently known for its integrative cognitive functions (Schmahmann, 2019). Indeed, theories of cerebellar dysfunction in schizophrenia point to impaired coordinated integration of stimuli, also known as cognitive dysmetria (Andreasen et al., 1998; Schmahmann, 2019). Finally, this domain contained the lowest number of studies and a high heterogeneity which points to an important gap in the literature and may indicate high variability in the tasks used to assess attention, which has been previously noted to lead to opposing results (Hoonakker et al., 2017).

4.2.3. Working memory

This domain was significantly associated with three networks: the DAN driven by the IFG opercularis, the SOM driven by the superior temporal gyrus, and the VAN by the superior frontal gyrus. This emergence of attentional networks (DAN, VAN) is not unexpected given that most tasks assessing WM require goal- and stimulus-directed processing (Moreau and Champagne-Lavau, 2014; Nuechterlein et al., 2004). Contribution of the superior temporal gyrus, part of the SOM, may reflect the auditory nature of several WM tasks (e.g., traditional digit span). No other network survived FDR correction although FPN and LIM were both found to have high numbers of correlations in the literature (21 and 14 respectively). Functional studies have pointed to an association between the FPN, more specifically the dorsolateral prefrontal cortex, and the DMN with WM in schizophrenia (Godwin et al., 2017; Kelly et al., 2019). The lack of association with the FPN is striking, particularly given the importance of the dorsolateral prefrontal cortex in WM via region of interest studies. Notably, the superior frontal gyrus, which did emerge as driving the association between the DAN and WM, overlaps anatomically with the dorsolateral prefrontal cortex. Other possibilities include the DLPFC association with WM being primarily of a functional nature or being obscured due to WM task variability. The lack of structural studies examining brain regions categorized in the DMN (none found in our review) indicates directions for future research. Another expected correlation of WM that we found was with the cerebellum, thought to be one of the important regions of working memory (Vandervert et al., 2007). Finally, due to its function in learning and memory (Andersen et al., 2006), it was also expected that the hippocampus would be significantly correlated with WM, which was supported by our findings.

4.2.4. Verbal learning and memory

VM was significantly associated with two networks, the FPN driven by the dorsolateral and middle frontal gyrus, and the VAN driven by the superior frontal gyrus. These findings support previous evidence indicating an association between VM and thinning of the frontal cortex in schizophrenia patients (Antonova et al., 2004; Guimond et al., 2016) as well as a reduced volume of prefrontal regions (Antonova et al., 2004). As expected due to its importance in memory, the hippocampus was also significantly associated with VM as shown previously (Antoniades et al., 2018; Guimond et al., 2016). However, the amygdala, usually involved in the emotional tagging of memories, did not significantly correlate with VM. This was not due to a lack of research investigating the association but is consistent with the general absence of emotional content in the tasks typically used to assess VM. Finally, the LIM, which includes parahippocampus and entorhinal cortex (input and output regions for the hippocampus, respectively; Foster et al. (2019)) was correlated with VM but did not retain significance following FDR correction. This may point to subnetworks or modules of LIM preferentially related to VM.

4.2.5. Visual learning and memory

VisM was significantly associated with the FPN, due to a strong correlation with the dorsolateral prefrontal cortex, and the VIS network, driven by a significant association with the fusiform gyrus. We expected the VisM-VIS association since this network is specific to visual processing and has been observed previously (Antonova et al., 2004; Kelly et al., 2019). The particular association between the fusiform gyrus, known for its involvement in facial recognition (Weiner and Zilles, 2016), and VisM may be due to studies assessing VisM with facial recognition tasks. Previous reviews also pointed to the prefrontal cortex as a processing and integration area for visual information (Antonova et al., 2004; Kelly et al., 2019), which is supported by the current findings. Four other networks were investigated in this domain but were nonsignificant. Although this effect can be explained by a small number of correlations for three of the networks (DMN, SOM, VAN), it is not the case for the LIM network which included 17 associations in the literature. Thus, it could be that the tasks assessing VisM have no emotional or reward component that would impact memory encoding or retrieval. This could also be the case for the nonsignificant association with the amygdala. In contrast, the cerebellum, implicated in facial recognition (Andreasen and Pierson, 2008), and the hippocampus, involved in memory, was significantly associated with VisM.

4.2.6. Reasoning and executive function

This domain, which is considered a higher-level domain encompassing several cognitive processes (e.g., SP, ATT; Nuechterlein et al., 2004), was significantly associated with all seven networks. Some of the strongest contributing regions to these findings included anterior cingulate cortex (DMN), IFG pars opercularis (DAN), middle frontal gyrus (FPN), orbitofrontal cortex (LIM), claustrum (SOM), BANKSTS (VAN), and inferior occipital lobe (VIS). The widespread brain regions associated with the domain likely reflects the many different processes engaged during reasoning and executive function tasks and the interrelation of this domain with other cognition domains, as has been noted in previous reviews (Antonova et al., 2004; Rüsch et al., 2008). Contrary to the previous domains, evidence of publication bias was found for R&EF at the overall level which had very few reported nonsignificant correlations. R&EF was also found to be significantly correlated with the hippocampus and the amygdala, centres of memory and emotional processing. As mentioned, this domain is multidimensional and was thus expected to recruit those subcortical regions (Rüsch et al., 2008). However, the cerebellum did not pass FDR correction which was surprising. Indeed, we would expect that as an integrative hub of cognitive processes, the cerebellum would be engaged during problem solving and executive functions which utilize multiple domains. Indeed, the “error detection” and cognitive coordination functions of the cerebellum are thought to be important for R&EF (Schmahmann, 2019).

4.2.7. Social cognition

Like R&EF, SC was also associated with all networks, confirming previous studies about these two domains potentially sharing neural correlates due to their higher-order nature (Moreau and Champagne-Lavau, 2014). However, the regions driving these network associations differed between the two cognitive domains. One pertinent example is the LIM, for which reasoning and executive function was associated with orbitofrontal cortex, while social cognition was associated with the parahippocampal gyrus, a region known for its encoding and retrieval function in memory and its proximity to the hippocampus (Diederen et al., 2010). Other SC-network correlations were driven by posterior cingulate gyrus (DMN), superior parietal lobule (DAN), IFG pars triangularis (FPN), superior temporal gyrus (SOM), middle cingulate gyrus (VAN), and middle occipital gyrus (VIS). These findings may point to distinct subnetworks subserving REAS&EF and SC in

schizophrenia.

The extensive structural abnormalities observed are consistent with previous reviews and studies identifying multiple subdomains of SC and related structures (Buck et al., 2016; Fujiwara et al., 2015; Green et al., 2015). SC also contained the strongest correlation with overall brain regions relative to the other domains. Clear divisions of tasks assessing SC allowed us to divide the domain into emotion processing and theory of mind, which are among the most frequently studied in schizophrenia (Savla et al., 2013), finding that both domains contributed to these overall findings. These strong correlations may be additional evidence of the publication bias found in this domain. Concerning other structures, the amygdala, responsible for emotional processing, and the hippocampus, involved in the memory component of some tasks, were significantly correlated with SC. The high heterogeneity of this domain is also evidenced by the significant difference between the low- and high- quality studies.

4.2.8. *Verbal fluency*

VF was associated only with the DMN driven by the inferior temporal gyrus, which is known for its function in auditory and speech processing (Takahashi et al., 2011). Verbal fluency measures are frequently related to or combined within SP and ATT (Nuechterlein et al., 2004; Ojeda et al., 2010), and SP also showed an association with the DMN and particularly the inferior temporal gyrus; however, overlapping associations between these domains in other networks could not be determined due to few associations reported in the literature. The hippocampus was non- significant, but the cerebellum showed a significant association with VF. As mentioned, the cerebellum is involved in speed of processing and integration of information. It would be expected to have a strong correlation with VF especially since previous studies have found that VF is related to SP in healthy controls (Ojeda et al., 2010). Publication bias present in this domain as well as non-significant differences between low- and high- quality studies could be evidence that there are a lot of similarities in methodologies between included studies.

4.3. *Strengths & limitations*

The current meta-analysis brings together the vast literature on brain structure and cognition in schizophrenia in an effort to provide a reliable reference for the field and inform on gaps in the literature. We assessed the risk of bias for studies in the literature for each of the eight domains as well as the quality of the studies based on several criteria relevant to the field. The use of the random effects model and the quality assessment also remediated the high heterogeneity found in domains. Additionally, leveraging networks to investigate structure-cognition associations is an approach that brings the previous literature up to the current state of the field and provides interesting future research directions. Visualizing both the networks and the associated brain regions provides a multidimensional understanding of the associations between brain structure and cognition.

However, there were some limitations to this study. First, meta-analyses are prone to diluted summary effects when combining multiple studies with different methodologies. Though our overall meta-analyses combined all identified brain regions and metrics per domain, the emergence of significant effects across all domains speaks to the strength of the observed associations in schizophrenia. In addition, our network subgroup analyses aimed to address this heterogeneity in a way that incorporates biologically meaningful brain architecture. Second, we performed a large number of subgroup analyses to pinpoint brain structure-cognition associations across domains and networks. To remediate this, we included corrections for multiple comparisons and report only corrected results. Also, due to the nature of the network analyses we wanted to perform, we excluded general regions (i.e., lobes) or other structures (i.e., ventricles, thalamus, nucleus accumbens), which may hold relevant associations with cognitive domains. We may also consider additional criteria that could distinguish low- and high-quality studies. For example, previous domain-specific meta-analyses found that covariates including medication duration, IQ and the duration of memory recall based on different tests and the tasks themselves may impact results (Antoniades et al., 2018; Knowles et al., 2010). These and other potential factors were not consistently assessed in the literature and could not be included in the current study. Moreover, cognitive tests measuring complex functions (e.g., reasoning and executive function) also recruit other cognitive processes (e.g., attention, speed of processing) to some degree. We categorized measures by their primary cognitive domain in this meta-analysis; however, future studies should consider using more "pure" measures of cognitive domains (e.g., Trail-Making Test B-A) to better isolate brain structure and function underlying lower- and higher-order cognitive domains. Finally, there was a substantial bias in the morphological metrics reported by studies. There is a very large literature on volume changes in relation to cognition in schizophrenia but relatively few investigations about other metrics including cortical thickness, surface area and density. The partiality of the literature limits our understanding of the neurobiological underpinnings of cognitive deficits in schizophrenia and should be explored in future research.

4.4. *Conclusion*

The current findings suggest strong associations between the most commonly assessed cognitive domains and overall brain structure in schizophrenia and provide insight into network associations and potential hub regions within those networks contributing to specific cognitive domains. We found that the number of networks associated with a given domain was often indicative of the complexity of that domain. We also identified multiple associations between the amygdala, the hippocampus, and the cerebellum with cognition in schizophrenia. The use of functional networks as a map for topographical studies yielded novel results and shed light on gaps in the literature concerning certain brain structures and biases that should be considered for some domains. We looked at structure mapped onto functional networks but investigating connectivity and between-network associations could be equally, if not more, important given the overlap between cognitive domains and associated brain networks. Moreover, the question of whether structurally defined brain networks (e.g., via morphometric graph measures) map onto functional networks warrants further investigation. Additionally, future studies should focus on determining which of cortical thickness or surface area drives the volumetric changes robustly reported in the literature. More research in this area is also necessary with first-episode psychosis or at-risk populations in order to determine whether these structural and network associations with cognition are present in early stages of psychosis, which would provide a deeper understanding of the neurodevelopmental aspects of the disorder.

Role of funding source

This study was supported by grants from the Canadian Institutes of Health Research and the Otsuka/Lundbeck Alliance. Salary awards include postdoctoral fellowship from the Canadian Institutes of Health Research (CIHR) for author KML and James McGill Professorship from McGill University and Research Chair from the FRQS for author ML. The funding sources had no role in the study design, analysis, or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Data availability

No data was used for the research described in the article.
Data will be made available on request.
All data is within the manuscript and figure.

Declaration of Competing Interest

ML reports grants from Otsuka Lundbeck Alliance, diaMentis, personal fees from Otsuka Canada, personal fees from Lundbeck Canada, grants and personal fees from Janssen, and personal fees from MedAvante-Prophase, outside the submitted work. Authors MK, PH, DRC, and KML declare no conflict of interests.

Acknowledgements

The authors would like to acknowledge the contribution of Vanessa McGrory (VM) and Cai Li (CL) during the article selection process and the quality control of data extraction. We would also like to thank Geneviève Sauvé for her invaluable help during the analysis of the results, Gabrielle Pochiet for her help during the setting of the meta-analysis and Élisabeth Thibaudeau for her insight into social cognition.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.11.034.

References

Alsop, D.C., Detre, J.A., Golay, X., Günther, M., Hendrikse, J., Hernandez-Garcia, L., et al., 2015. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn. Reson. Med. 73 (1), 102–116.

Andersen, P., Morris, R., Amaral, D., Bliss, T., O'Keefe, J., 2006. The Hippocampus Book. Oxford University Press.

Andreasen, N.C., Pierson, R., 2008. The role of the cerebellum in schizophrenia. Biol. Psychiatry 64 (2), 81–88. https://doi.org/10.1016/j.biopsych.2008.01.003.

Andreasen, N.C., Paradiso, S., O'Leary, D.S., 1998. 'Cognitive dysmetria' as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr. Bull. 24 (2), 203–218.

Antoniades, M., Schoeler, T., Radua, J., Valli, I., Allen, P., Kempton, M.J., McGuire, P., 2018. Verbal learning and hippocampal dysfunction in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. 86, 166–175. https://doi.org/10.1016/j.neubiorev.2017.12.001.

Antonova, E., Sharma, T., Morris, R., Kumari, V., 2004. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr. Res. 70 (2), 117–145. https://doi.org/10.1016/j.schres.2003.12.002.

Bassett, D.S., Sporns, O., 2017. Network neuroscience. Nat. Neurosci. 20 (3), 353–364. https://doi.org/10.1038/nn.4502.

Belur, J., Tompson, L., Thornton, A., Simon, M., 2018. Interrater reliability in systematic review methodology: exploring variation in coder decision-making. Sociol. Methods Res. https://doi.org/10.1177/0049124118799372, 0049124118799372.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. JR Statist. Soc. B 57, 289–300. Find this article online.

Brébion, G., Amador, X., Smith, M.J., Gorman, J.M., 1998. Memory impairment and schizophrenia: the role of processing speed. Schizophr. Res. 30 (1), 31–39. https://doi.org/10.1016/S0920-9964(97)00123-0.

Buck, B.E., Healey, K.M., Gagen, E.C., Roberts, D.L., Penn, D.L., 2016. Social cognition in schizophrenia: factor structure, clinical and functional correlates. J. Ment. Health 25 (4), 330–337. https://doi.org/10.3109/09638237.2015.1124397.

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Yeo, B.T.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (5), 2322–2345. https://doi.org/10.1152/jn.00339.2011.

Cochran, W.G., 1950. The comparison of percentages in matched samples. Biometrika 37 (3/4), 256–266.

Crespo-Facorro, B., Barbadillo, L., Pelayo-Terán, J.M., Rodríguez-Sánchez, J.M., 2007. Neuropsychological functioning and brain structure in schizophrenia. Int. Rev. Psychiatry 19 (4), 325–336. https://doi.org/10.1080/09540260701486647.

Diederen, K.M.J., Neggers, S.F.W., Daalman, K., Blom, J.D., Goekoop, R., Kahn, R.S., Sommer, I.E.C., 2010. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. Am. J. Psychiatry 167 (4), 427–435. https://doi.org/10.1176/appi.ajp.2009.09040456.

Easterbrook, P.J., Gopalan, R., Berlin, J.A., Matthews, D.R., 1991. Publication bias in clinical research. Lancet 337 (8746), 867–872. https://doi.org/10.1016/0140-6736(91)90201-Y.

Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.

Eickhoff, S.B., Yeo, B.T.T., Genon, S., 2018. Imaging-based parcellations of the human brain. Nat. Rev. Neurosci. 19 (11), 672–686. https://doi.org/10.1038/s41583-018-0071-7.

Evans, A.C., 2013. Networks of anatomical covariance. NeuroImage 80, 489–504. https://doi.org/10.1016/j.neuroimage.2013.05.054.

Foster, C.M., Kennedy, K.M., Hoagey, D.A., Rodrigue, K.M., 2019. The role of hippocampal subfield volume and fornix microstructure in episodic memory across the lifespan. Hippocampus 29 (12), 1206–1223. https://doi.org/10.1002/hipo.23133.

Fragkos, K.C., Tsagris, M., Frangos, C.C., 2014. Publication Bias in meta-analysis: confidence intervals for Rosenthal's fail-safe number. Int. Sch. Res. Notices 2014, 825383. https://doi.org/10.1155/2014/825383.

Fujiwara, H., Yassin, W., Murai, T., 2015. Neuroimaging studies of social cognition in schizophrenia. Psychiatry Clin. Neurosci. 69 (5), 259–267. https://doi.org/10.1111/pcn.12258.

Gennatas, E.D., Avants, B.B., Wolf, D.H., Satterthwaite, T.D., Ruparel, K., Ciric, R., et al., 2017. Age-related effects and sex differences in gray matter density, volume, mass, and cortical thickness from childhood to young adulthood. J. Neurosci. 37 (20), 5065. https://doi.org/10.1523/JNEUROSCI.3550-16.2017.

Glover, G.H., Mueller, B.A., Turner, J.A., van Erp, T.G.M., Liu, T.T., Greve, D.N., Potkin, S.G., 2012. Function biomedical informatics research network recommendations for prospective multicenter functional MRI studies. J. Magn. Reson. Imaging 36 (1), 39–54. https://doi.org/10.1002/jmri.23572.

Godwin, D., Ji, A., Kandala, S., Mamah, D., 2017. Functional connectivity of cognitive brain networks in schizophrenia during a working memory task. Front. Psychiatry 8 (294). https://doi.org/10.3389/fpsyt.2017.00294.

Green, M.F., Horan, W.P., Lee, J., 2015. Social cognition in schizophrenia. Nat. Rev. Neurosci. 16 (10), 620–631. https://doi.org/10.1038/nrn4005.

Guimond, S., Chakravarty, M.M., Bergeron-Gagnon, L., Patel, R., Lepage, M., 2016. Verbal memory impairments in schizophrenia associated with cortical thinning. Neuroimage Clin. 11, 20–29. https://doi.org/10.1016/j.nicl.2015.12.010.

Gur, C.R., Ragland, J.D., Gur, R.E., 1997. Cognitive changes in schizophrenia-a critical look. Int. Rev. Psychiatry 9 (4), 449–458. https://doi.org/10.1080/09540269775312.

Gwet, K.L., 2008. Computing inter-rater reliability and its variance in the presence of high agreement. Br. J. Math. Stat. Psychol. 61 (1), 29–48. https://doi.org/10.1348/000711006x126600.

Hall, J.A., Rosenthal, R., 2018. Choosing between random effects models in meta-analysis: units of analysis and the generalizability of obtained results. Soc. Personal. Psychol. Compass 12 (10), e12414. https://doi.org/10.1111/spc3.12414.

Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12 (3), 426–445. https://doi.org/10.1037/0894-4105.12.3.426.

Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.

Hoonakker, M., Doignon-Camus, N., Bonnefond, A., 2017. Sustaining attention to simple visual tasks: a central deficit in schizophrenia? A systematic review. Ann. N. Y. Acad. Sci. 1408 (1), 32–45. https://doi.org/10.1111/nyas.13514.

James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., et al., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392 (10159), 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7.

Kahn, R.S., Keefe, R.S.E., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70 (10), 1107–1112. https://doi.org/10.1001/jamapsychiatry.2013.155.

Kahn, R.S., Sommer, I.E., Murray, R.M., Meyer-Lindenberg, A., Weinberger, D.R., Cannon, T.D., et al., 2015. Schizophrenia. Nat. Rev. Dis. Primers 1, 15067. https://doi.org/10.1038/nrdp.2015.67.

Kelly, S., Guimond, S., Lyall, A., Stone, W.S., Shenton, M.E., Keshavan, M., Seidman, L.J., 2019. Neural correlates of cognitive deficits across developmental phases of schizophrenia. Neurobiol. Dis. 131, 104353. https://doi.org/10.1016/j.nbd.2018.12.013.

Kirschner, M., Shafiei, G., Markello, R.D., Makowski, C., Talpalaru, A., Hodzic-Santor, B., et al., 2020. Latent clinical-anatomical dimensions of schizophrenia. Schizophr. Bull. 46 (6), 1426–1438. https://doi.org/10.1093/schbul/sbaa097.

Kitchen, H., Rofail, D., Heron, L., Sacco, P., 2012. Cognitive impairment associated with schizophrenia: a review of the humanistic burden. Adv. Ther. 29 (2), 148–162. https://doi.org/10.1007/s12325-012-0001-4.

Klein, A., Tourville, J., 2012. 101 labeled brain images and a consistent human cortical labeling protocol. Front. Neurosci. 6 (171) https://doi.org/10.3389/fnins.2012.00171.

Knowles, E.E.M., David, A.S., Reichenberg, A., 2010. Processing speed deficits in schizophrenia: reexamining the evidence. Am. J. Psychiatry 167 (7), 828–835. https://doi.org/10.1176/appi.ajp.2010.09070937.

Knowles, E.E.M., Weiser, M., David, A.S., Glahn, D.C., Davidson, M., Reichenberg, A., 2015. The puzzle of processing speed, memory, and executive function impairments in schizophrenia: fitting the pieces together. Biol. Psychiatry 78 (11), 786–793. https://doi.org/10.1016/j.biopsych.2015.01.018.

Koshiyama, D., Fukunaga, M., Okada, N., Yamashita, F., Yamamori, H., Yasuda, Y., et al., 2018. Role of subcortical structures on cognitive and social function in schizophrenia. Sci. Rep. 8 (1), 1183. https://doi.org/10.1038/s41598-017-18950-2.

Lavigne, K.M., Sauvé, G., Raucher-Chéné, D., Lepage, M., 2020. Remote Cognitive Assessment in Severe Mental Illness: A Scoping Review.

Lepage, M., Bodnar, M., Bowie, C., 2014. Neurocognition: clinical and functional outcomes in schizophrenia. Can. J. Psychiatry 59 (1), 5–12. https://doi.org/10.1177/070674371405900103.

Lesh, T.A., Niendam, T.A., Minzenberg, M.J., Carter, C.S., 2011. Cognitive control deficits in schizophrenia: mechanisms and meaning. Neuropsychopharmacology 36 (1), 316–338. https://doi.org/10.1038/npp.2010.156.

Lipsey, M.W., Wilson, D.B., 2001. Practical Meta-analysis. SAGE publications, Inc.

Makowski, C., Lewis, J.D., Khundrakpam, B., Tardif, C.L., Palaniyappan, L., Joober, R., et al., 2020. Altered hippocampal centrality and dynamic anatomical covariance of intracortical microstructure in first episode psychosis. Hippocampus 30 (10), 1058–1072.

Marder, S.R., 2006. The NIMH-MATRICS project for developing cognition-enhancing agents for schizophrenia. Dialogues Clin. Neurosci. 8 (1), 109–113.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7) e1000097.

Moreau, N., Champagne-Lavau, M., 2014. Théorie de l'esprit et fonctions exécutives dans la pathologie. [Theory of mind and executive functions in pathology]. Rev. Neuropsychol. 6 (4), 276–281. https://doi.org/10.3917/rne.064.0276.

Müller, V.I., Cieslik, E.C., Laird, A.R., Fox, P.T., Radua, J., Mataix-Cols, D., et al., 2018. Ten simple rules for neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 84, 151–161. https://doi.org/10.1016/j.neubiorev.2017.11.012.

Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72 (1), 29–39. https://doi.org/10.1016/j.schres.2004.09.007.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., et al., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165 (2), 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042.

Ojeda, N., Sánchez, P., Peña, J., Elizagárate, E., Yoller, A.B., Larumbe, J., et al., 2010. Verbal fluency in schizophrenia: does cognitive performance reflect the same underlying mechanisms in patients and healthy controls? J. Nerv. Ment. Dis. 198 (4).

Park, H.-J., Friston, K., 2013. Structural and functional brain networks: from connections to cognition. Science 342 (6158), 1238411. https://doi.org/10.1126/science.1238411.

Pereira, T.V., Patsopoulos, N.A., Salanti, G., Ioannidis, J.P., 2010. Critical interpretation of Cochran's Q test depends on power and prior assumptions about heterogeneity. Res. Synth. Methods 1 (2), 149–161.

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., Mechelli, A., 2011. Dysconnectivity in schizophrenia: Where are we now? Neurosci. Biobehav. Rev. 35 (5), 1110–1124. https://doi.org/10.1016/j.neubiorev.2010.11.004.

Poldrack, R.A., Baker, C.I., Durnez, J., Gorgolewski, K.J., Matthews, P.M., Munafò, M.R., et al., 2017. Scanning the horizon: towards transparent and reproducible neuroimaging research. Nat. Rev. Neurosci. 18 (2), 115.

Potvin, S., 2020. LA MÉTA-ANALYSE. Méthodes qualitatives, quantitatives et mixtes, 2e édition: dans la recherche en sciences humaines. sociales et de la santé.

Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86 (3), 638.

Rüsch, N., Tebartz van Elst, L., Valerius, G., Büchert, M., Thiel, T., Ebert, D., et al., 2008. Neurochemical and structural correlates of executive dysfunction in schizophrenia. Schizophr. Res. 99 (1), 155–163. https://doi.org/10.1016/j.schres.2007.05.024.

Savla, G.N., Vella, L., Armstrong, C.C., Penn, D.L., Twamley, E.W., 2013. Deficits in domains of social cognition in schizophrenia: a meta-analysis of the empirical evidence. Schizophr. Bull. 39 (5), 979–992. https://doi.org/10.1093/schbul/sbs080.

Schaefer, J., Giangrande, E., Weinberger, D.R., Dickinson, D., 2013. The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophr. Res. 150 (1), 42–50. https://doi.org/10.1016/j.schres.2013.07.009.

Schmahmann, J.D., 2019. The cerebellum and cognition. Neurosci. Lett. 688, 62–75. https://doi.org/10.1016/j.neulet.2018.07.005.

Seidman, L.J., Shapiro, D.I., Stone, W.S., Woodberry, K.A., Ronzio, A., Cornblatt, B.A., et al., 2016. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American prodrome longitudinal study. JAMA Psychiatry 73 (12), 1239–1248. https://doi.org/10.1001/jamapsychiatry.2016.2479.

Shafiei, G., Markello, R.D., Makowski, C., Talpalaru, A., Kirschner, M., Devenyi, G.A., et al., 2020. Spatial patterning of tissue volume loss in schizophrenia reflects brain network architecture. Biol. Psychiatry 87 (8), 727–735. https://doi.org/10.1016/j.biopsych.2019.09.031.

Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophr. Res. 49 (1), 1–52. https://doi.org/10.1016/S0920-9964(01)00163-3.

Silva, P.H.R., Spedo, C.T., Baldassarini, C.R., Benini, C.D., Ferreira, D.A., Barreira, A.A., Leoni, R.F., 2019. Brain functional and effective connectivity underlying the information processing speed assessed by the Symbol Digit Modalities test. NeuroImage 184, 761–770. https://doi.org/10.1016/j.neuroimage.2018.09.080.

Sukumar, N., Sabesan, P., Anazodo, U., Palaniyappan, L., 2020. Neurovascular uncoupling in schizophrenia: a bimodal meta-analysis of brain perfusion and glucose metabolism. Front. Psychiatry 11 (754). https://doi.org/10.3389/fpsyt.2020.00754.

Takahashi, T., Zhou, S.-Y., Nakamura, K., Tanino, R., Furuichi, A., Kido, M., et al., 2011. A follow-up MRI study of the fusiform gyrus and middle and inferior temporal gyri in schizophrenia spectrum. Prog. Neuropsychopharmacol. Biol. Psychiatry 35 (8), 1957–1964. https://doi.org/10.1016/j.pnpbp.2011.07.009.

The EndNote Team, 2013. Endnote [64 bit]. Clarivate., Philadelphia, PA.

Uddin, L.Q., Yeo, B.T.T., Spreng, R.N., 2019. Towards a universal taxonomy of macro-scale functional human brain networks. Brain Topogr. 32 (6), 926–942. https://doi.org/10.1007/s10548-019-00744-6.

van Erp, T., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., et al., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol. Psychiatry 21 (4), 547–553. https://doi.org/10.1038/mp.2015.63.

van Erp, T.G.M., Walton, E., Hibar, D.P., Schmaal, L., Jiang, W., Glahn, D.C., et al., 2018. Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through Meta analysis (ENIGMA) consortium. Biol. Psychiatry 84 (9), 644–654. https://doi.org/10.1016/j.biopsych.2018.04.023.

Van Rheenen, T.E., Rossell, S.L., 2014. An empirical evaluation of the MATRICS Consensus Cognitive Battery in bipolar disorder. Bipolar Disord. 16 (3), 318–325. https://doi.org/10.1111/bdi.12134.

Vandervert, L.R., Schimpf, P.H., Liu, H., 2007. How working memory and the cerebellum collaborate to produce creativity and innovation. Creat. Res. J. 19 (1), 1–18. https://doi.org/10.1080/10400410709336873.

Ventura, J., Hellemann, G.S., Thames, A.D., Koellner, V., Nuechterlein, K.H., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. Schizophr. Res. 113 (2), 189–199. https://doi.org/10.1016/j.schres.2009.03.035.

Weiner, K.S., Zilles, K., 2016. The anatomical and functional specialization of the fusiform gyrus. Neuropsychologia 83, 48–62. https://doi.org/10.1016/j.neuropsychologia.2015.06.033.

Wongpakaran, N., Wongpakaran, T., Wedding, D., Gwet, K.L., 2013. A comparison of Cohen's Kappa and Gwet's AC1 when calculating inter-rater reliability coefficients: a study conducted with personality disorder samples. BMC Med. Res. Methodol. 13 (1), 61. https://doi.org/10.1186/1471-2288-13-61.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., et al., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (3), 1125–1165. https://doi.org/10.1152/jn.00338.2011.

Yeo, D.J., Wilkey, E.D., Price, G.R., 2017. The search for the number form area: a functional neuroimaging meta-analysis. Neurosci. Biobehav. Rev. 78, 145–160. https://doi.org/10.1016/j.neubiorev.2017.04.027.