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White matter alterations and cognitive correlates in the early course of schizophrenia

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**WHITE MATTER ALTERATIONS AND COGNITIVE CORRELATES IN THE
EARLY COURSE OF SCHIZOPHRENIA**

by

RACHAL R. HEGDE

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Approved by

First Reader

Carole Palumbo, Ph.D.
Research Associate Professor of Neurology

Second Reader

Sinéad Kelly, Ph.D.
Instructor of Psychiatry
Beth Israel Deaconess Medical Center
Brigham and Women's Hospital
Harvard Medical School

Third Reader

Synthia Guimond, Ph.D.
Assistant Professor of Psychiatry
The Royal's Institute of Mental Health Research
University of Ottawa

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ABSTRACT

Background: White matter (WM) aberrations have been broadly characterized in schizophrenia using standard diffusion tensor imaging (DTI) techniques. The present study aims to distinguish WM alterations in the early course of schizophrenia using advanced diffusion measures of free-water corrected fractional anisotropy (FAt) and free-water fractional volume (FW), in addition to examining their association with neurocognition, social cognition, and clinical measures. We report baseline results from a longitudinal study investigating the effects of cognitive enhancement therapy (CET) on brain structure and function in schizophrenia.

Methods: The sample consisted of 46 early course schizophrenia patients and 20 healthy controls. Diffusion-weighted images were processed using a free-water imaging pipeline, that separately models diffusion of water in tissue (FAt) and the extracellular space (FW). Tract-Based Spatial Statistics was performed on the FAt and FW diffusion tensor maps and average measures from 24 bilateral regions of interest (ROIs) were extracted. We examined WM structural differences between patients and controls and further investigated WM relations to neurocognition, social cognition, and clinical measures specifically in schizophrenia.

Results: Patients showed significant FAt reductions in the body of the corpus callosum, posterior thalamic radiation (PTR), cingulate gyrus, anterior corona radiata, corpus callosum, and corona radiata and FW elevations in the posterior corona radiata (PCR), uncinate fasciculus (UNC), and PTR compared to controls. For patients, positive correlations between FAt and working memory were observed in the PCR and fornix & stria terminalis (FXST). Negative associations between FW and attention/vigilance were observed in the UNC. Positive correlations between FAt and theory of mind (ToM) were observed in average whole-brain and FXST. Negative associations between FW and ToM were observed in average whole-brain and PCR. Positive correlations between FW and negative symptom severity were observed in the external capsule.

Conclusion: Using free-water imaging, we report WM aberrations and FW elevations in the early course of schizophrenia in addition to neural correlates associated with cognition and clinical measures. Future investigations on the longitudinal effects of CET are warranted for a greater understanding of the underlying neural correlates of clinical manifestations in schizophrenia.

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LIST OF ABBREVIATIONS

ACR	Anterior Corona Radiata
AD	Axial Diffusivity
ALIC	Anterior Limb of Internal Capsule
BCC	Body of Corpus Callosum
BICEPS	Brain Imaging Cognitive Enhancement and Early Schizophrenia
CC	Corpus Callosum
CET	Cognitive Enhancement Therapy
CGC	Cingulate Gyrus
CGH	Hippocampal Cingulum
CR	Corona Radiata
CRT	Cognitive Remediation Therapy
CST	Corticospinal Tract
DTI	Diffusion Tensor Imaging
EC	External Capsule
FA	Fractional Anisotropy
FAt	Free-water Corrected Fractional Anisotropy
FDR	False Discovery Rate
FSL	FMRIB Software Library
FW	Free-Water
FWI	Free-Water Imaging
FX	Fornix

FXST.....	Fornix & Stria Terminalis
GCC.....	Genu of the Corpus Callosum
GM.....	Gray Matter
HC.....	Healthy Control
IC.....	Internal Capsule
IFO.....	Inferior Fronto-occipital Fasciculus
MRI.....	Magnetic Resonance Imaging
MATRICES...	Measurement and Treatment Research Improve Cognition in Schizophrenia
MD.....	Mean Diffusivity
NIMH.....	National Institute of Mental Health
PCR.....	Posterior Corona Radiata
PLIC.....	Posterior Limb of Internal Capsule
PTR.....	Posterior Thalamic Radiation
RLIC.....	Retrolenticular Part of Internal Capsule
RD.....	Radial Diffusivity
SANS.....	Scale for the Assessment of Negative Symptoms
SAPS.....	Scale for the Assessment of Positive Symptoms
SCC.....	Splenium of Corpus Callosum
SCR.....	Superior Corona Radiata
SFO.....	Superior Fronto-occipital Fasciculus
SLF.....	Superior Longitudinal Fasciculus
SS.....	Sagittal Striatum

SZ.....Schizophrenia
UNC.....Uncinate Fasciculus
WM.....White Matter

INTRODUCTION

Classifying Schizophrenia

Schizophrenia (SZ) is a chronic, complex neuropsychiatric disorder affecting approximately 1% of the global population (American Psychiatric Association, 2013). According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and as further summarized in Table 1, diagnostic criteria for SZ must include two or more of the following for a significant duration of time over 1-month: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, or negative symptoms. Furthermore, at least one of the symptoms must include one of the first three criteria listed in Table 1 (American Psychiatric Association, 2013; Freedman, 2003).

Table 1: Diagnostic Features of Schizophrenia. Table with criteria for diagnosing schizophrenia taken from Freedman, 2003.

At least two of the following characteristic symptoms lasting at least one month: Delusions Hallucinations Disorganized speech Grossly disorganized or catatonic behavior Negative symptoms, such as affective flattening (Only one characteristic symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts or two or more voices conversing with each other) Dysfunction in work, interpersonal relationships, or self-care throughout most of the illness; a level of functioning markedly below the level the patient had achieved or might reasonably have been predicted to achieve before the onset of illness Any of the above symptoms lasting, in full or attenuated form, at least six months Mood disorder not prominent after the onset of psychotic symptoms (if psychotic symptoms always occur during mood disturbance severe enough to meet the criteria for bipolar disorder or a major depressive disorder, the diagnosis is schizoaffective disorder) Illness not due to a medication or other medical conditions or substance abuse Illness not part of autism or another pervasive developmental disorder

SZ symptoms are further classified into positive and negative symptoms. Positive symptoms are defined as psychotic behaviors, including: hallucinations, delusions, thought disorders, and movement disorders. Negative symptoms are defined as disruptive emotional and behavioral processing such as: flat affect, anhedonia, avolition, and alogia (American Psychiatric Association, 2013).

Structural Brain Abnormalities in Schizophrenia

Although there is a limited understanding of the pathophysiology of SZ, potential mechanisms underlying progressive brain volume deficits include abnormal neurotransmission, neuropil abnormalities, and stress-related hypothalamic-pituitary-adrenal functional hyperactivity (Busatto, Zanetti, Schaufelberger, & Crippa, 2010). Several histopathological studies have also consistently identified the presence of altered myelin and oligodendrocyte pathology in SZ (Davis et al., 2003; Konrad & Winterer, 2007; Segal, Koschnick, Slegers, & Hof, 2007; Torrey, Webster, Knable, Johnston, & Yolken, 2000).

As brain structural abnormalities are commonly associated with SZ, several longitudinal magnetic resonance imaging (MRI) studies have compared neuronal structure of SZ participants with healthy controls (HC) in order to investigate disruptions in neuronal development. SZ typically appears to display enlarged lateral and third ventricles, increased cerebrospinal fluid space, and volumetric reduction in several brain regions such as the hippocampus, superior temporal cortex, frontal and temporal gray matter (GM), as well as abnormalities in white matter (WM) (Busatto et al., 2010; Freedman, 2003). These

defining features exemplify disrupted neuronal development, some of which are thought to predate the onset of SZ illness.

Van Erp et al. (2015) conducted a meta-analysis investigating patterns of subcortical brain abnormalities between SZ and HC reporting SZ had localized volumetric reductions in the hippocampus, amygdala, thalamus, accumbens, and total intracranial volume. Van Erp et al. (2018) further went on to conduct a meta-analysis examining cortical thickness and surface area abnormalities between SZ and HC. The study noted neuroanatomical abnormalities in SZ are regionally specific with SZ having a widespread thinner cortex and reduced cortical surface area.

Evidence from prior studies have also reported correlations between WM volume and volumetric reduction in both temporal and frontal lobe regions suggesting potential relations between WM and GM pathology (Kubicki et al., 2007). Several studies have additionally shown correlations between volumetric reductions in frontal GM and WM brain regions with the degree of psychotic severity (Banaj et al., 2018). As neuronal circuitry and functional connectivity between various brain regions rely on WM, underlying cerebral WM connections are considered to contribute to the pathophysiology of SZ (Ellison-Wright & Bullmore, 2009; Hong & Kochunov, 2014; Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2014).

In 1906, Carl Wernicke initially proposed SZ to be associated with disruptive association fibers in the brain and recently SZ has been hypothesized to be a disorder of disrupted connectivity involving aberrant communication between functional brain regions (Karl J. Friston, 1998; Karl J. Friston, 2002). Current advancements in neuroimaging

techniques and analysis including functional connectivity and diffusion tensor imaging (DTI) have allowed research to further support this hypothesis (K. J. Friston & Frith, 1995).

These defining features exemplify disrupted neuronal development, some of which are thought to predate the onset of SZ illness (Busatto et al., 2010; Freedman, 2003). Through neuroimaging analysis, studies have shown correlations between structural abnormalities and clinical manifestations including cognitive deficits and neuropsychiatric impairments. Thus, greater insight into understanding the process through which brain connectivity disruptions lead to neuropsychiatric impairments and clinical manifestations via WM alterations are warranted.

White Matter and Diffusion Tensor Imaging

Diffusion MRI has revolutionized diagnostic imaging. Diffusion-weighted imaging (DWI) evaluates the microarchitecture of the brain by providing signal contrast based on the quantification of water diffusion in brain tissue, a method known as Brownian motion. Water diffusion is defined as isotropic when diffusion is considered equal in all directions and defined as anisotropic when diffusion is restricted in certain directions (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996).

Diffusion Tensor Imaging (DTI) allows for the assessment of spatial organization of tissue orientation by examining the three-dimensional shape of diffusion as a 3x3 matrix comprising a diffusion tensor representing location, orientation, and anisotropy of the brain's WM tracts (Kubicki et al., 2007; Pierpaoli et al., 1996). Fractional anisotropy (FA), considered an index of neuronal integrity, reflects both the organization of WM tracts and

myelination of axon fibers. Secondary measures include mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). MD is the average diffusion rate across all fiber orientations within a tract; AD is considered to be an indicator of myelination as it measures the diffusion rate along fiber orientations of an axon; and RD measures the diffusion rate perpendicular to the fiber orientation (Pierpaoli et al., 1996).

From DTI analyses, studies have found decreased FA in prefrontal and temporal lobes, aberrations within fiber bundles connecting both regions, and recurrent WM tract disruptions in patients with SZ (Karlsgodt, Sun, & Cannon, 2010; Kubicki et al., 2007; Wheeler & Voineskos, 2014). These disruptions of WM networks contribute to the structural connectivity abnormalities present from preclinical to chronic stages of SZ, resulting in significant clinical manifestations and cognitive deficits (Canu, Agosta, & Filippi, 2015; Karlsgodt, Sun, et al., 2010; Kubicki et al., 2007; Szeszko et al., 2007).

Free-Water Imaging

DTI indices, such as FA, are highly sensitive to biological pathologies such as axonal degeneration and elevated extracellular free-water (FW). FW can be defined as diffusing water molecules free of restriction or hinderance from surrounding tissues, and therefore, are not recommended to be regarded as specific markers for WM microstructural changes (Alexander, Lee, Lazar, & Field, 2007; Assaf & Pasternak, 2008; Pierpaoli et al., 1996).

Free-water imaging (FWI) is a novel technique offering increased sensitivity to the detection of structural changes in WM as it corrects for FW contamination in the DTI

acquisition schemes. FW is considered to be an indicator of extracellular changes due to the contribution of pathologies such as atrophy, edema, or neuroinflammation (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009). Free-water corrected FA (FAt) reductions are found to be limited to frontal lobe WM while FW is shown to exhibit global increases in first-episode patients (Lyall et al., 2017; Pasternak et al., 2012). Chronic SZ, however, is found to be associated with widespread FAt reductions with limited FW elevations, indicating increased WM deterioration (Oestreich et al., 2017a; Pasternak, Westin, Dahlben, Bouix, & Kubicki, 2015). The application of FWI allows researchers to identify WM changes in SZ related to developmental change, cognition, and symptomatology. Investigating neural correlates with measures of FAt and FW is critical as prior findings have revealed extracellular changes play a significant role in early stages of SZ and progress to increased WM deterioration overtime.

Cognitive Deficits in Schizophrenia

Neurocognitive impairments are often present prior to the onset of psychosis and are prevalent in domains of attention, executive function, memory, learning, and social cognition (Barch, 2004; Nuechterlein et al., 2004). Cognitive decline in SZ is a significant risk factor to consider as neuropsychological deficits serve as potential indicators of the severity and progression of SZ. The US National Institute of Mental Health (NIMH) developed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus which includes attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem

solving, processing speed, and social cognition subdomains relevant to SZ research in order to address cognitive decline in SZ (Nuechterlein et al., 2008).

In addition to neurocognitive impairments, social cognition appears to be a major determinant of functional disabilities in schizophrenia (Brekke, Hoe, Long, & Green, 2007; Fett et al., 2011; Michael Foster Green, Kern, Braff, & Mintz, 2000; Kennedy & Adolphs, 2012) and is further thought to be a mediator of the relation between neurocognition and functional outcome (Couture, Penn, & Roberts, 2006). Social cognitive impairments have been well documented in SZ, yet there is a limited understanding of social cognitive domains. Social cognitive processes which are known to be impaired in SZ include mentalizing, social perception, social knowledge, attributional biases, and emotion (Michael F Green, Olivier, Crawley, Penn, & Silverstein, 2005). Mentalizing, also known as theory of mind (ToM), is of great interest and is suggested to be a greater predictor of functional outcome than neurocognition (Fett et al., 2011), making it an important therapeutic target for early intervention.

White Matter Correlates of Cognitive Deficits in SZ

DTI studies have shown that altered structural WM integrity in frontal and temporal brain regions and FA reduction in numerous WM tracts in frontal-temporal connections are correlated with cognitive impairment in executive functioning (Haller, Padmanabhan, Lizano, Torous, & Keshavan, 2014; Wheeler & Voineskos, 2014). WM forms a crucial component of the human connectome (Sporns, Tononi, & Kötter, 2005) and transfers information within dispersed neural networks functioning in cognitive operations (Filley

& Fields, 2016). Working memory impairments have been directly linked to WM alterations in SZ (Karlsgodt, Kochunov, et al., 2010; Karlsgodt, Niendam, Bearden, & Cannon, 2009; Nazeri et al., 2013). Previous studies have reported associations between neurocognitive impairments and specific WM regions and processing speed (Kochunov et al., 2016; Kochunov et al 2017; Roalf et al., 2013). Furthermore, Lyall et al. (2017) is the only present study to examine neurocognitive correlates in relation to FW in SZ and proposes elevated extracellular FW as a predictor of better functional outcomes in first episode psychosis.

While there is a growing literature on WM alterations in relation to neurocognition in SZ, little is known about WM alterations and social dysfunction. Research suggests that the frontal cortical regions and the corpus callosum play essential roles in social functioning (Koshiyama et al., 2018; Miyata et al., 2010). To our knowledge, no study has examined social cognitive correlates of FAt and FW in SZ.

Cognitive Remediation Therapy

Although antipsychotics have been helpful in the treatment of positive symptoms, they are unable to treat negative symptoms, cognitive impairments, and functional deficits in SZ (Patel, Cherian, Gohil, & Atkinson, 2014). This has led to a substantial interest in developing non-pharmacological interventions in SZ (Andreou & Moritz, 2016). Cognitive remediation therapy (CRT) is a behavioral training-based non-pharmacological intervention designed to improve cognitive functioning and behavior with a further aim to improve psychosocial and community functioning (Keshavan, Vinogradov, Rumsey,

Sherrill, & Wagner, 2014). The majority of CRT programs typically focuses on targeting either neurocognition or social cognition but some cognitive therapies like cognitive enhancement therapy (CET) focus on a more integrated approach of both neurocognitive and social cognitive factors for maximal treatment outcomes (Eack et al., 2009; Hogarty GE, Flesher S, Ulrich R, & et al, 2004). CET includes elements of executive training as well as sociocognitive components in order to address cognitive dysfunction and social difficulties underlying positive and negative symptomatology in schizophrenia (Hogarty & Flesher, 1999).

CRT has proven to be an effective intervention for cognitive impairments in addition to improving daily functioning in SZ (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Collectively, evidence from neuroimaging studies indicate both structural and functional changes in major prefrontal brain regions (Keshavan et al., 2014; Thorsen, Johansson, & Løberg, 2014). CRT is a promising option as abnormal prefrontal cortical activity tends to be associated with impairments in several cognitive domains (Keshavan et al., 2014; Thorsen et al., 2014). Although knowledge of the underlying neural mechanisms of CRT is limited, evidence from studies indicate strengthened compensatory structures and promotion of growth and connectivity through neuroplasticity, supporting the beneficial abilities of CRT to preserve both neurobiological and cognitive factors (Minzenberg MJ, Laird AR, Thelen S, Carter CS, & Glahn DC, 2009).

While there is a growing literature on CRT's effects on GM, Penadés et al. (2013) is the only present study to examine CRT's effects on WM changes in SZ, reporting evidence for increased FA in the genu of the corpus callosum and the posterior thalamic

radiation after CRT. Structural changes further support the hypothesized beneficial effects of CRT's aim to minimize the progressive degradation of brain damage in SZ. However, in order to develop effective treatment strategies for SZ, a greater understanding of neural substrates susceptible to CRT are warranted.

SPECIFIC AIMS

Currently there is a limited understanding of the etiology and underlying neurobiological basis of SZ. As SZ is proposed to be a disorder of dysconnectivity, neural network disruptions may lead to cognitive impairments and clinical manifestations. A greater understanding of the microstructural WM alterations and their associations to both cognitive and clinical correlates may lead to earlier diagnosis and treatment to reduce the severity and progression of SZ symptoms.

This study first aims to delineate WM structural abnormalities between SZ and HC using FAt and FW measures through DTI analysis. We hypothesize that early course SZ will have greater FAt reductions and elevated FW compared to HC. In order to better understand structural changes in SZ at various stages, early course SZ will further be classified into early stage and later stage SZ based on a 2-year duration of illness cut-off.

Our secondary objective is to examine WM relations to neurocognition, social cognition, and clinical symptom severity in SZ. As the literature is limited with regards to the association of FAt and FW measures with clinical manifestations in SZ, we further aim to identify potential neural correlates associated with cognition and clinical measures which may serve as biomarkers for predicting improvements following CET.

Identification of WM aberrations in the early stages of SZ may be a fundamental pathophysiological mechanism underlying clinical presentation of SZ before the appearance of clinical symptoms. Thus, a greater understanding of these neurobiological mechanisms is critical for developing intervention strategies to preserve brain structure and function in SZ.

METHODS

Subjects

Participants were recruited through the National Institute of Mental Health (NIMH) funded study: Brain Imaging, Cognitive Enhancement and Early Schizophrenia (BICEPS). Participants were selected as part of a baseline assessment of a dual site (Boston and Pittsburgh) randomized-controlled study (NCT #01561859) examining the effects of CET in early course SZ. The study received ethics committee approval from The University of Pittsburgh and Beth Israel Deaconess Medical Center. Participants signed a written, informed consent prior to participation.

This sample included 46 patients within the early course SZ and 20 HC (see Table 2). HC participants had an average age of 25.5 (SD=4.2) years and patients had an average age of 25.9 (SD=6.4) years. Samples of controls and patients were 60.9% and 75% males, respectively. The mean age of onset and duration of illness across SZ were 21.9 (SD=5.1) and 3.9 (SD=2.1) years, respectively. The mean total SAPS and SANS across SZ were 0.3 (SD=0.4) and 1.3 (SD=0.8), respectively. The CPZ mean dose equivalent was 390.3 mg/day (SD=264.1).

Inclusion criteria required participants to be between 18-45 years of age, have an IQ>80 as assessed using the WASI-II (Hays, Reas, & Shaw, 2002), an ability to read at a 6th grade level or higher, and speak fluent English. Patients were included if they had a diagnosis of SZ or schizoaffective disorder and was further verified using the SCID interview, duration of psychotic symptoms <8 years, stabilized on antipsychotic medication (assessed via SCID and medical history). Exclusion criteria included reported

history of significant neurological disorders that may produce cognitive impairment (e.g., seizure disorder, traumatic brain injury), persistent suicidal or homicidal behavior, recent history of substance abuse or dependence (within the past 3 months), MRI contraindications, and decisional incapacity requiring a guardian. HC were also excluded if they had major psychiatric illness or family history of psychosis.

Neuropsychological & Clinical Test Measures

Neurocognition

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) cognitive battery for clinical trials was administered to assess for neurocognitive functioning. The cognitive battery measures reasoning & problem solving, processing speed, attention & vigilance, working memory, verbal learning & memory, visual learning & memory, and social cognition (Nuechterlein et al., 2004). The social cognition score was evaluated from the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) total score (Mayer, Salovey, Caruso, & Sitarenios, 2003). T-scores were corrected for age and sex and composite scores were then derived for each domain.

Social Cognition

As social cognition is multidimensional, we implemented three factors of social cognition, specifically derived from the current sample of early course schizophrenia patients. These factors were determined from 11 validated data subsets assessing domains of social cognitive skills in 90 patients with early course schizophrenia and is further

described in detail in Mike et al. (2019). The three factors assess for Emotion Management, Theory of Mind (ToM), and Emotion Perception and classification of these domains was based on MATRICS recommendations (Green et al., 2005).

Clinical measures

Patients' positive and negative symptom severity were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), respectively. Higher scores on these measures indicate more severe symptomology.

Diffusion MR Procedures

Diffusion MRI scans were acquired at the University of Pittsburgh on a 3.0 T Siemens Trio Imaging Systems scanner. A total of 87 diffusion-weighted images were obtained from each subject. Multi-shell dMRI was acquired with 6 gradient directions at $b=100$ s/mm², 10 at 400 s/mm², and 80 at 900 s/mm² with 2mm isotropic voxels.

Image Acquisition and Processing

Free Water Imaging

The Free Water Imaging analysis pipeline was executed following the methods described in detail by Pasternak et al. (2009). Diffusion-weighted images were corrected for motion, eddy-current artifacts, and masking of the diffusion MRI. The FW imaging maps were generated by fitting the aligned diffusion-weighted images with a two-

compartment model comprising a FW compartment and a tissue compartment (Pasternak et al., 2009). The FW compartment accounts for the fractional volume of FW found in extracellular space whereas the tissue compartment accounts for the signal left after eliminating contribution of freely diffusing water. The FAt parameter enables more accurate estimations of tissue specific FA measures as the signal contribution from extracellular space is attenuated.

White Matter Processing

WM was investigated using whole-brain Tract-Based Spatial Statistics (TBSS) according to the ENIGMA-DTI Working Group protocol (<http://enigma.ini.usc.edu/ongoing/dtiworking-group/>). A detailed description of the TBSS procedure is provided by Smith et al. (2006). FA images from all participants were co-registered into the ENIGMA-DTI template (Jahanshad et al., 2013). Each participant's aligned FA image was then projected onto the ENIGMA-DTI skeleton using non-linear registration creating a skeletonized FA map. Regions of interest (ROI) were parcellated from the ENIGMA-DTI target, defined according to the Johns Hopkins University WM atlas calculating average FA for each ROI (Mori et al., 2008; Oishi et al., 2008). We selected for all 24 bilateral ROIs and average FAt and FW across the entire skeleton. Mean FAt and FW values were extracted for all bilateral ROIs and whole brain. The 24 bilateral ROIs include: anterior corona radiata (ACR); anterior limb of internal capsule (ALIC); body of corpus callosum (BCC); corpus callosum (CC); cingulum (cingulate gyrus) (CGC); cingulum (hippocampal portion) (CGH); corona radiata (CR); corticospinal tract

(CST); external capsule (EC); fornix (FX); fornix & stria terminalis (FXST); genu of the corpus callosum (GCC); internal capsule (IC); inferior fronto-occipital fasciculus (IFO); posterior corona radiata (PCR); posterior limb of internal capsule (PLIC); posterior thalamic radiation (PTR); retrolenticular part of internal capsule (RLIC); splenium of corpus callosum (SCC); superior corona radiata (SCR); superior front-occipital fasciculus (SFO); superior longitudinal fasciculus (SLF); sagittal striatum (SS); and uncinate fasciculus (UNC).

Statistical Analysis

All statistical analyses were conducted using R (version 3.5.1, <https://www.r-project.org/>). We used t-tests and Chi square tests to compare demographic data between patients and controls.

To investigate group comparisons (2 levels: HC, SZ) for FAt and FW of bilateral tracts as well as for neurocognitive differences, we performed an analysis of variance (ANOVA). A Spearman correlation was also performed to assess the effects of illness duration. As early course schizophrenia displayed a bimodal distribution for duration of illness, we further separated the heterogeneity effects in early course schizophrenia into two subgroups: early stage (<2 years) and later stage (>2 years). A secondary ANOVA was run comparing early stage SZ, later stage SZ, and HC. Effect sizes were calculated with Cohen's d and age and sex were used as covariates for all analyses. Race and education were also included as covariates for neurocognitive performance. We chose to include education rather than IQ as a covariate for neurocognitive performance since education

was significantly different between patients and controls. For social cognitive performance, only race was included as an additional covariate as race has been shown to be linked to social cognitive performance in schizophrenia (Pinkham, Kelsven, Kouros, Harvey, & Penn, 2017).

We ran Spearman correlations correcting for ROIs within neurocognitive, social cognitive, and clinical measures to investigate associations between all ROIs and both cognitive and clinical correlates. All p -values were adjusted for False Discovery Rate (FDR) correction with an adjusted significance threshold of $p < 0.05$.

RESULTS

Demographics

As illustrated in Table 2, there were a total of 66 subjects (SZ=46, HC=20). Patients and controls were matched on age, sex, race, and IQ, but differed for education (Table 2).

Table 2. Sample Characteristics of the Comparisons Between SZ and HC Subjects

	SZ (n=46)		HC (n=20)		χ^2	p-value
	<u>N</u>		<u>N</u>			
Sex (Male/Female)	28/18		15/5		0.7	0.409
Race (CA/AA/OT)	29/14/3		14/5/1		3.9	0.278
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>	<u>F</u>	<u>p-value</u>
Age (years)	25.9	6.4	25.5	4.2	53.9	0.809
Education*	13.8	2.1	15.6	2.4	31.3	0.006
IQ	106.6	11.0	107.7	13.9	29.8	0.77
Age of Onset	21.9	5.7	-	-	-	-
Illness Duration	3.9	2.2	-	-	-	-
SAPS Total Score	0.3	0.4	-	-	-	-
SANS Total Score	1.3	0.8	-	-	-	-
Daily CPZ equivalents (mg/day)	390.3	264.1	-	-	-	-

Notes: SZ, Schizophrenia; HC, Healthy Controls; SD, Standard Deviation; AA, African American; CA, Caucasian; OT, Other; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; CPZ, Chlorpromazine; *, p<0.05.

White Matter Microstructural Differences in FAt and FW

Of the 25 regions, SZ showed FAt reductions in 6 regions. The largest effect sizes were detected in the BCC, followed by the PTR, CGC, ACR, CC, and the CR (Figure 2, Supplementary Table 1). However, effects did not survive FDR correction.

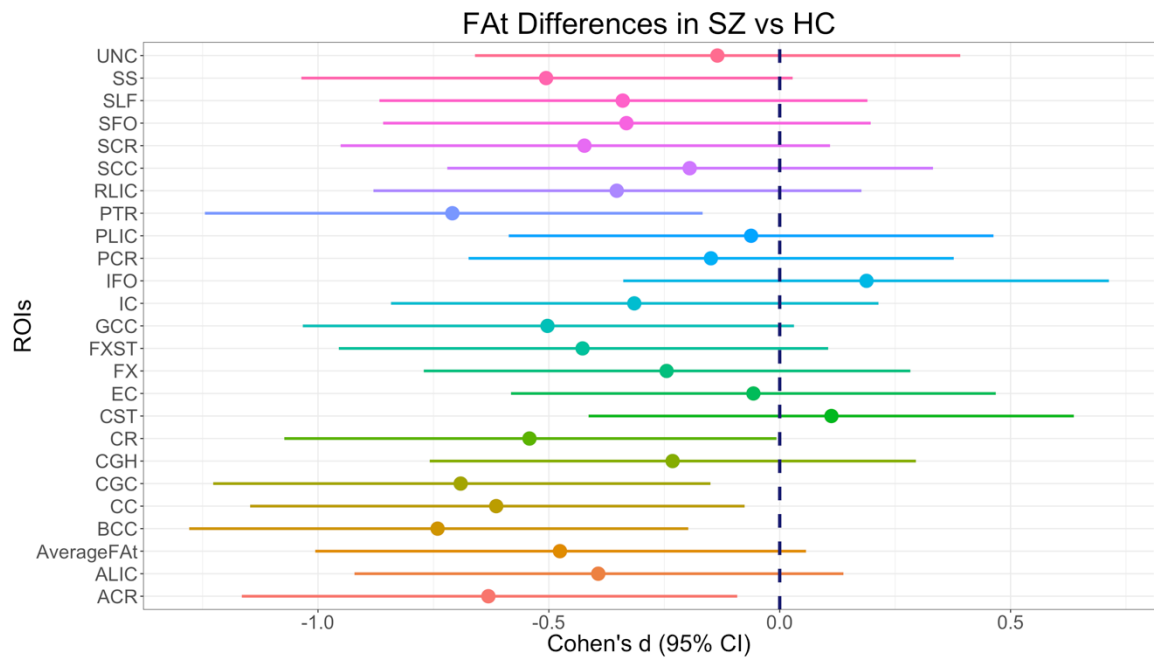


Figure 1. Effect sizes for FAt differences between SZ and HC. Circles indicate Cohen's d and horizontal lines indicate 95% confidence interval (CI). Data was covaried for age and sex. Displaying uncorrected p-values ($p < 0.05$).

SZ also showed elevated FW in 3 regions. The largest effect sizes were observed in the PCR, followed by the UNC, and the PTR (Figure 3, Supplementary Table 2). However, effects did not survive FDR correction.

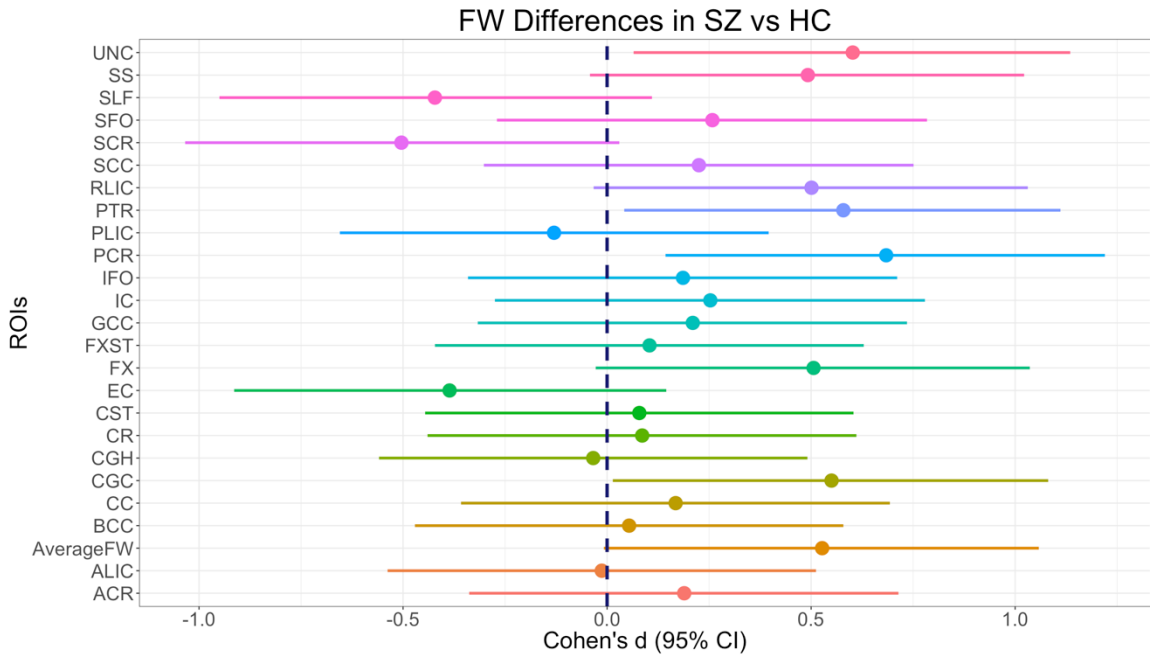


Figure 2. Effect sizes for FW differences between SZ and HC. Circles indicate Cohen's d and horizontal lines indicate 95% CI. Data was covaried for age and sex. Displaying uncorrected p-values ($p < 0.05$).

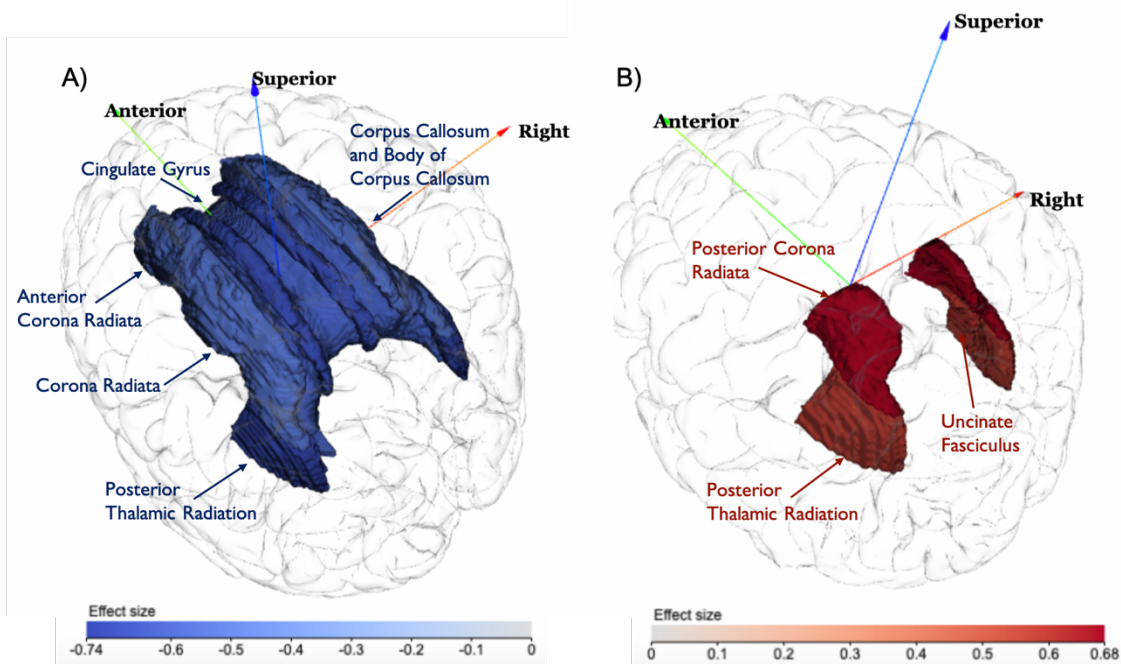


Figure 3. White matter microstructural differences in SZ compared to HC. Effect sizes between SZ and HC for A) FAt and B) FW. Colors indicate Cohen's d (adjusted for age and sex). Data visualization through ENIGMA-Viewer (Zhang et al., 2017).

White Matter Differences in FAt and FW in Relation to Illness Duration

To assess the potential impact of illness duration on WM changes in SZ, we carried out correlations between illness duration and FAt and FW. No significant associations were found for illness duration and age of onset for FAt and FW in SZ. The SZ group was then further divided into early (n=13) and later (n=33) stage subgroups in order to detect for subtle microstructural changes sensitive to duration of illness.

In the SZ sub-group analysis, no significant differences in FAt were detected between early stage SZ and HCs. However, early stage SZ showed significantly higher FAt

compared to later stage SZ in the BCC, followed by CGH, and average whole-brain FAt ($p < 0.05$, FDR correction). Furthermore, later stage SZ showed significant FAt reductions compared to HCs in the PTR, followed by the BCC, CGC, ACR, FXST, CR and average whole-brain FAt ($p < 0.05$, FDR correction) (Figure 4, Supplementary Table 3).

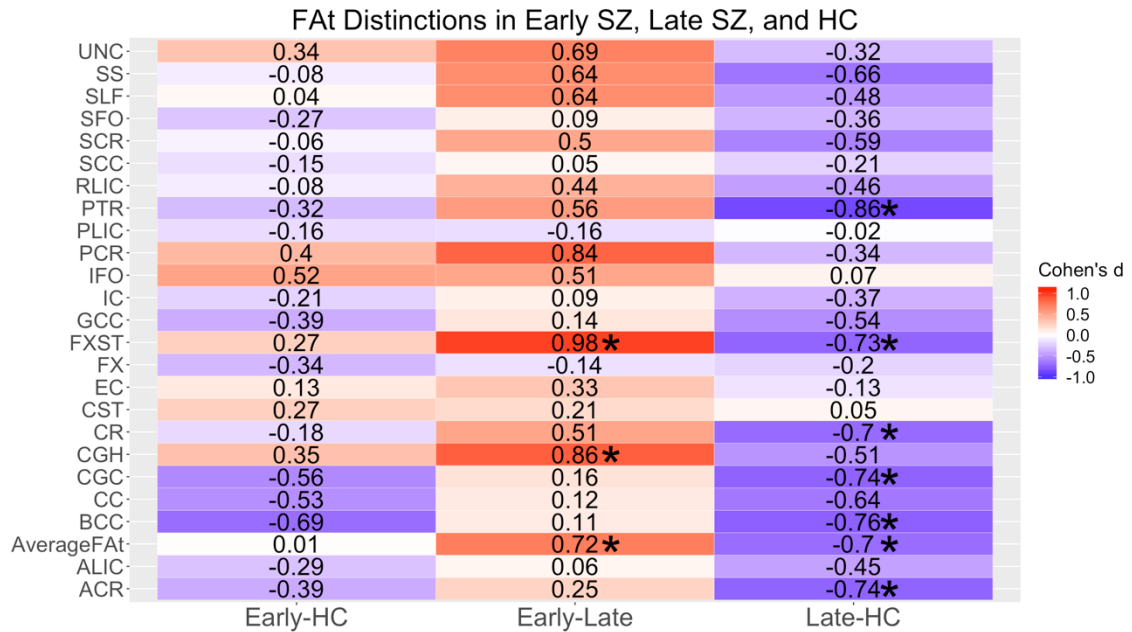


Figure 4. FAt distinctions between SZ stages and HC. Effect sizes for FAt measures in early stage SZ vs HC, early stage SZ vs later stage SZ, and later stage SZ vs HC. Data was covaried for age and sex. Cohen’s d referred by color legend. (* indicates $p < 0.05$, FDR correction).

FW in the FX was significantly elevated in early patients compared to HCs ($p < 0.05$, FDR correction). In comparison, later stage patients showed significantly elevated FW in the PCR compared to HC ($p < 0.05$, FDR correction) (Figure 5, Supplementary Table 4). No significant differences were detected between early and late patients after FDR correction.

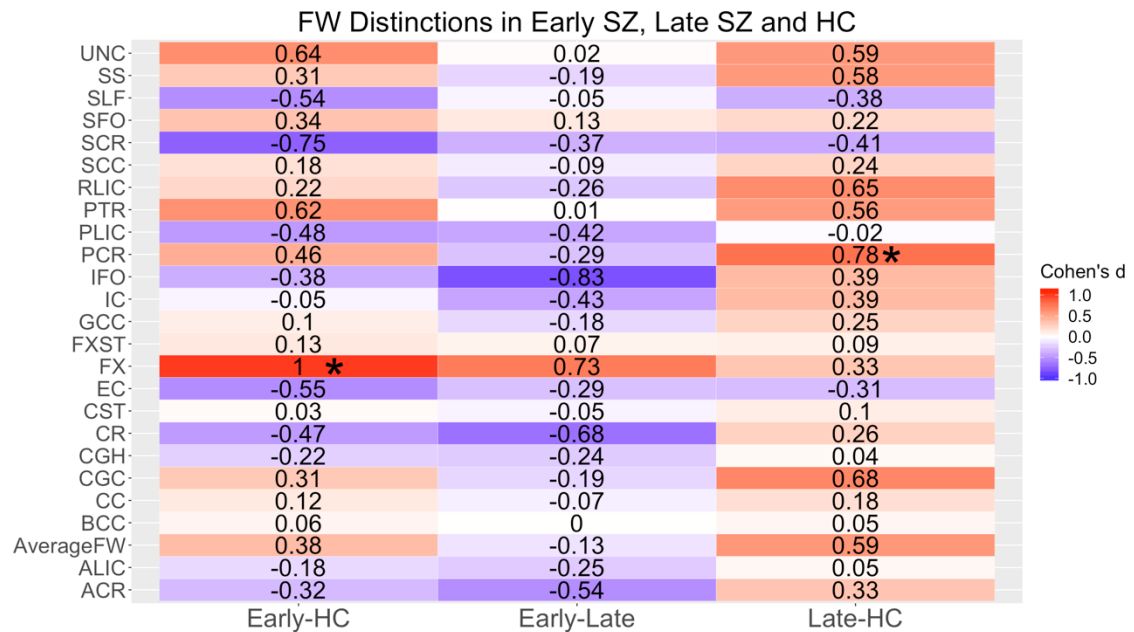


Figure 5. FW distinctions between SZ stages and HC. Effect sizes for FW measures in early stage SZ vs HC, early stage SZ vs later stage SZ, and later stage SZ vs HC. Data was covaried for age and sex. Cohen's d referred by color legend. (* indicates $p < 0.05$, FDR correction).

Neurocognitive Differences Between Schizophrenia and Healthy Controls

SZ performed lower in all cognitive domains in comparison to HC with the exception of the visual learning and memory domain. However, this finding did not reach statistical significance. SZ displayed significantly lower neurocognitive performance for speed of processing, verbal learning and memory, social cognition, and reasoning and problem solving ($p < 0.05$) (Figure 6, Supplementary Table 5). However, reasoning and problem solving did not survive after FDR correction.

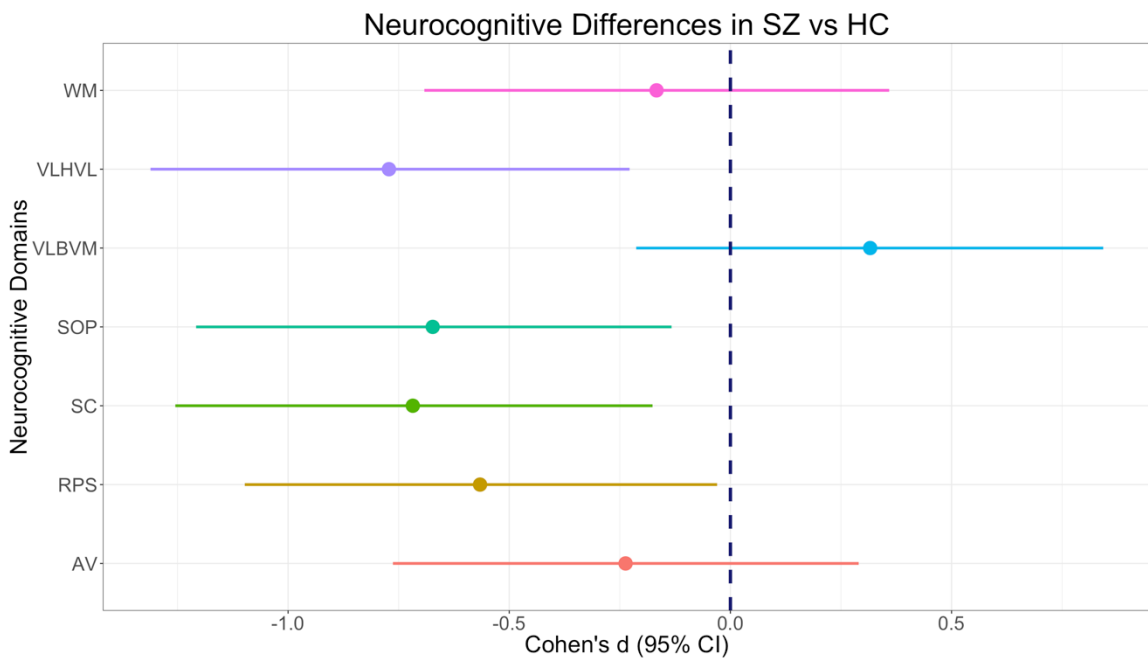


Figure 6. Effect sizes for neurocognitive differences between SZ and HC. Circles indicate Cohen's d and horizontal lines indicate 95% CI. Data was covaried for age, sex, race, and education. Displaying FDR corrected p-values ($p < 0.05$).

Relations Between White Matter and Neurocognition in Schizophrenia

To investigate whether WM changes were associated with neurocognition in SZ, we conducted correlations between neurocognitive domain scores and FAt and FW across all ROIs. Significant positive correlations were observed between working memory and FAt for CGH, FXST, and PCR ($p < 0.05$). However, only associations between working memory and FXST and PCR survived FDR correction (Figure 7, Supplementary Table 6).

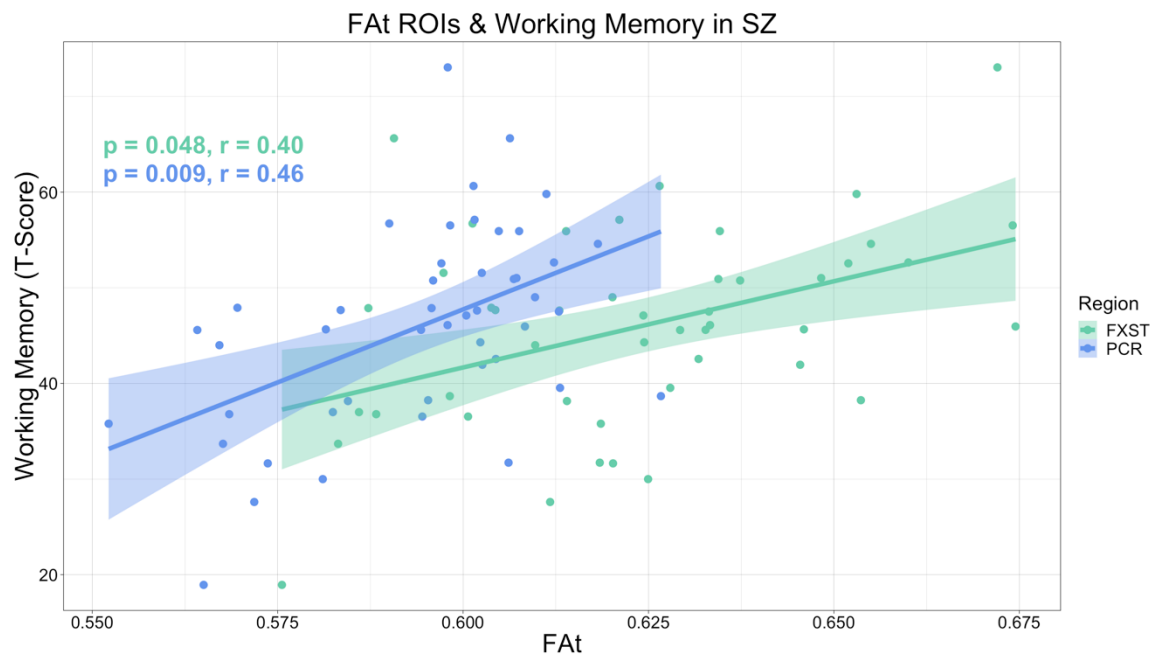


Figure 7. Significant ROIs associated with working memory in SZ. The FAt of the FXST and the PCR were positively correlated with working memory. Data was covaried for age, sex, race, and education. Displaying FDR corrected p-values ($p < 0.05$).

Significant negative correlations were observed between attention/vigilance and FW for the UNC ($p < 0.05$, FDR correction). Negative associations were also seen between working memory and FW for the CGH and PLIC. However, only associations between attention/vigilance and UNC survived FDR correction (Figure 8, Supplementary Table 6).

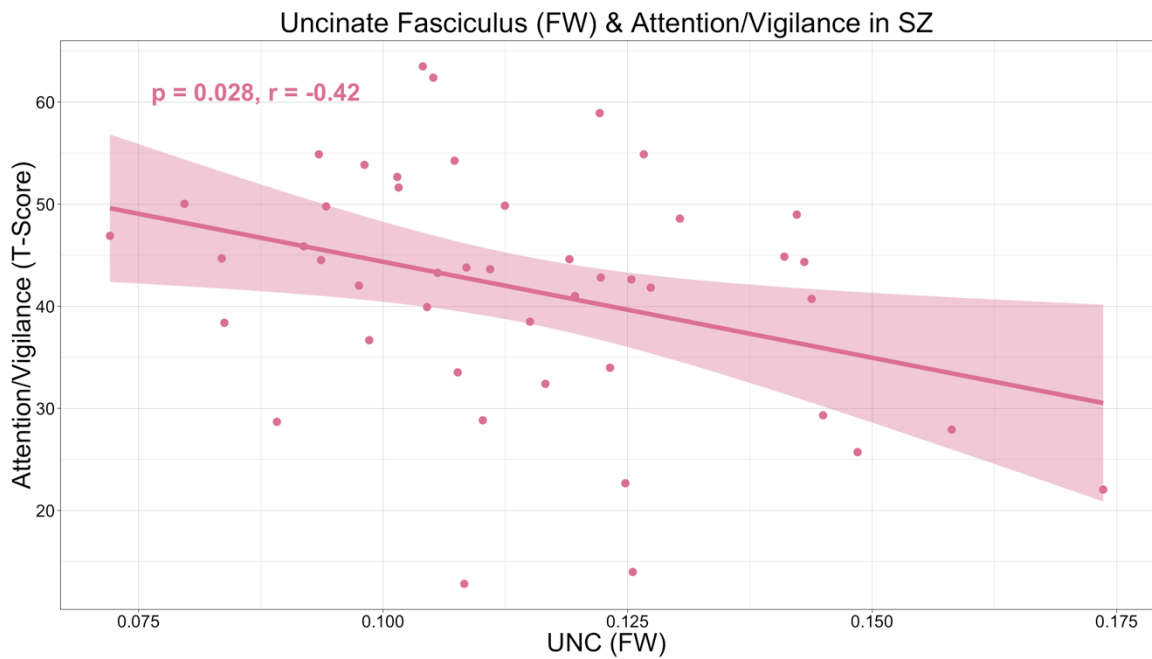


Figure 8. Uncinate Fasciculus (FW) & attention/vigilance in SZ. The FW of the UNC was negatively correlated with attention/vigilance. Data was covaried for age, sex, race, and education. Displaying FDR corrected p-values ($p < 0.05$).

Relations Between White Matter and Social Cognition in Schizophrenia

To investigate whether WM changes were associated with social cognition in SZ, we conducted correlations between three social cognition factors and FAt and FW across all ROIs. Positive correlations were observed between ToM and FAt for average whole-brain FAt, FXST, IC, PLIC, SCR, and UNC ($p < 0.05$) (Supplementary Table 7). However, only associations between ToM and FAt for average whole brain FAt and FXST survived FDR correction (Figure 9 & Figure 10).

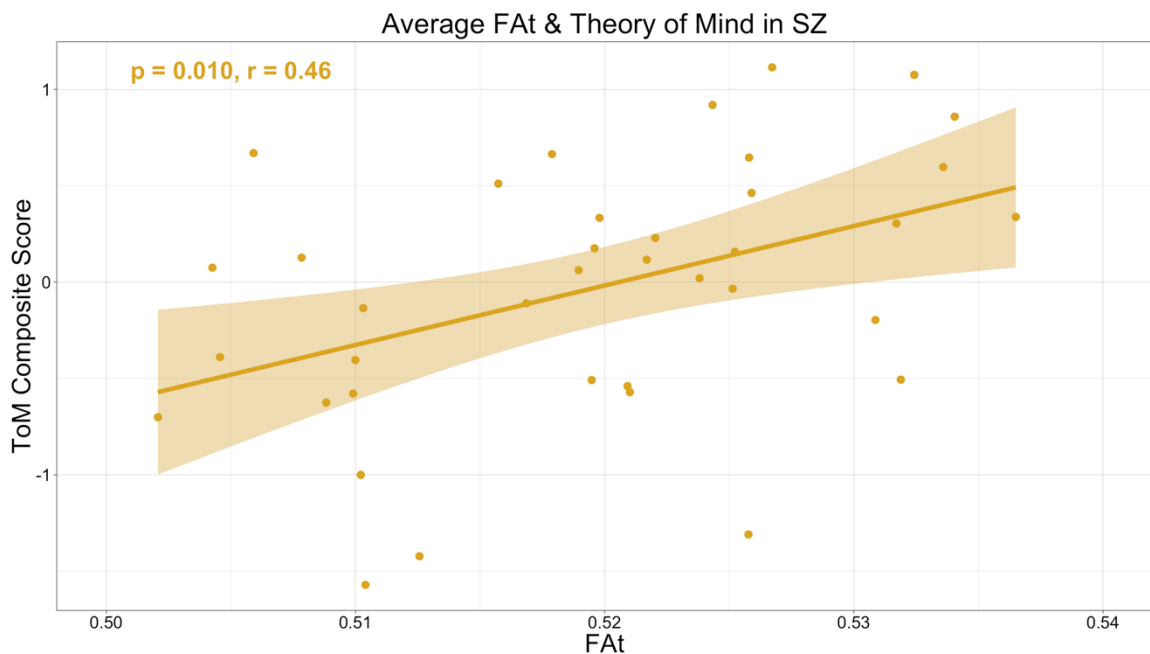


Figure 9. Average FAt & ToM in SZ. The average FAt was positively correlated with ToM. Data was covaried for age, sex, and race. Displaying FDR corrected p-values ($p < 0.05$).

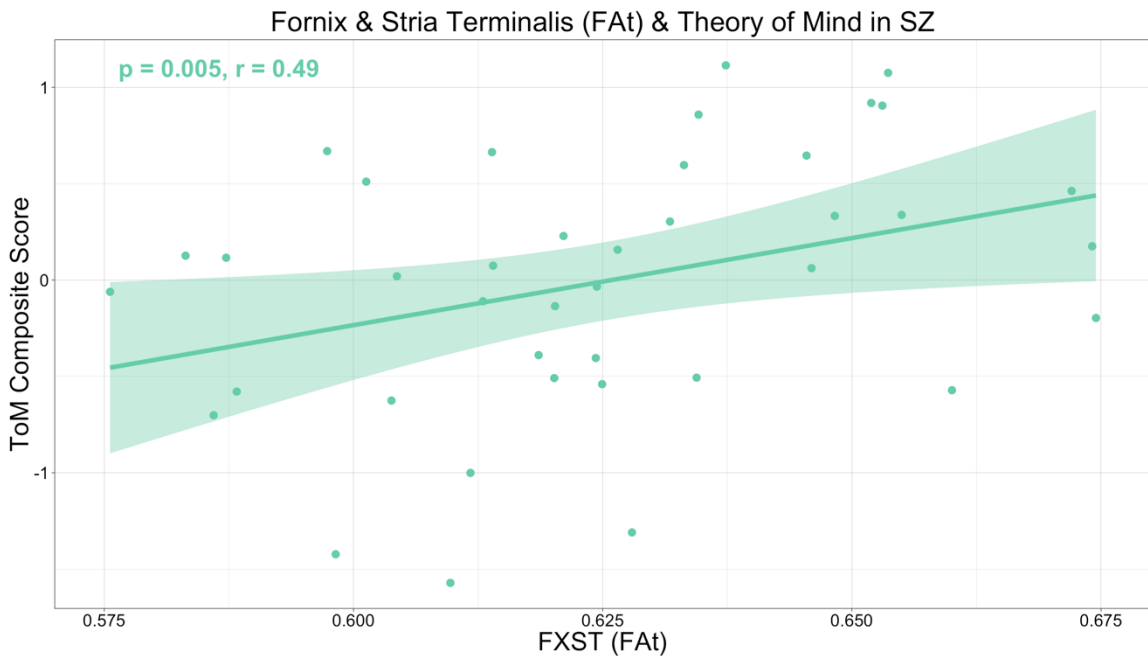


Figure 10. Fornix & Stria Terminalis (FAt) & ToM in SZ. The FAt of the FXST was positively correlated with ToM. Data was covaried for age, sex, and race. Displaying FDR corrected p-values ($P < 0.05$).

Negative correlations were observed between ToM and FW for average whole-brain, ACR, CGC, CR, CST, GCC, IC and PCR ($p < 0.05$) (Supplementary Table 8). Negative associations were also seen between emotion recognition and FW for the CGH. Only associations between ToM and FW for average whole-brain and PCR survived FDR correction (Figure 11 & Figure 12).

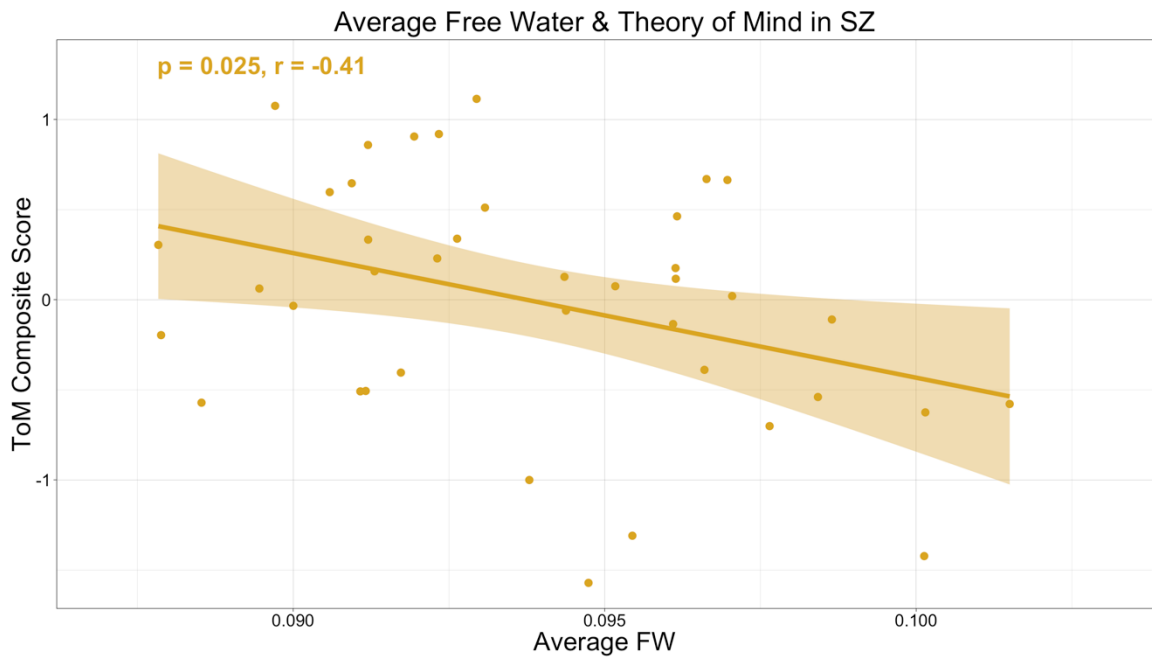


Figure 11. Average FW & ToM in SZ. The average FW was negatively correlated with ToM. Data was covaried for age, sex, and race. Displaying FDR corrected p-values ($p < 0.05$).

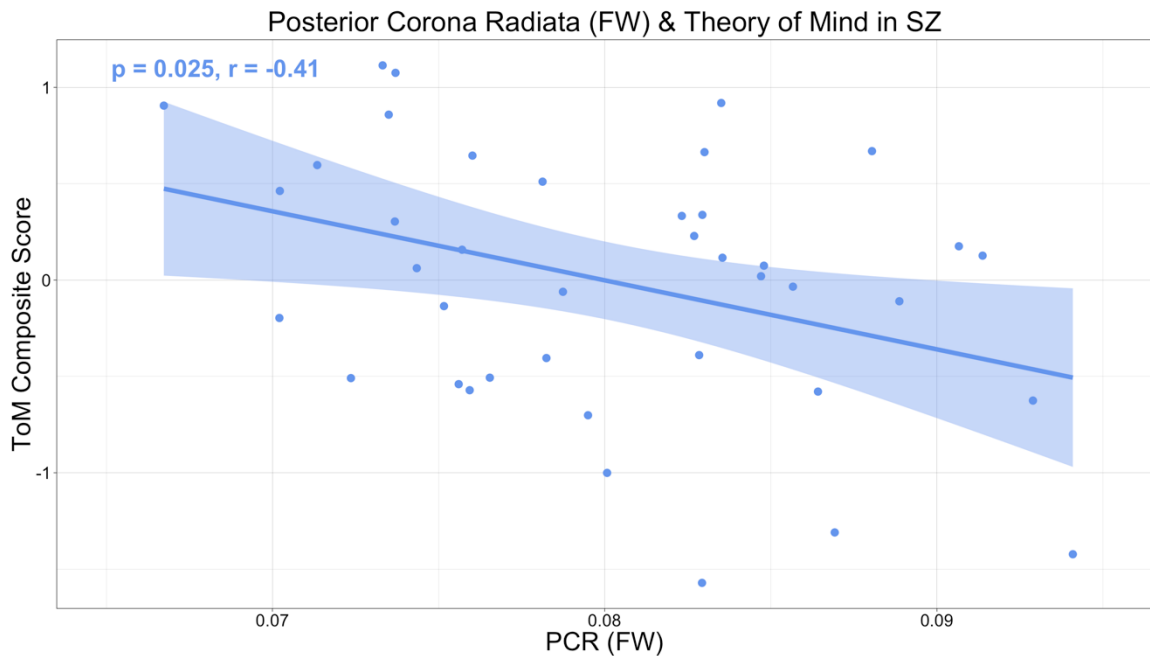


Figure 12. Posterior Corona Radiata (FW) & with ToM in SZ. The FW of the PCR was negatively correlated with ToM. Data was covaried for age, sex, and race. Displaying FDR corrected p-values ($p < 0.05$).

Relations Between White Matter and Clinical Symptomatology in Schizophrenia

To investigate whether WM alterations were correlated with positive and negative symptom severity in SZ, we conducted correlations between symptom severity scores from SAPS and SANS and FAt and FW across all ROIs. We saw positive correlations between the SAPS total score and BCC and SLF ($p < 0.05$) (Supplementary Table 9). However, these correlations did not survive after FDR correction. Significant positive correlations were observed for the EC and SANS total score for FW ($p < 0.05$, FDR correction) (Figure 13). No significant correlations were found for positive symptoms or CPZ equivalency in FAt and FW.

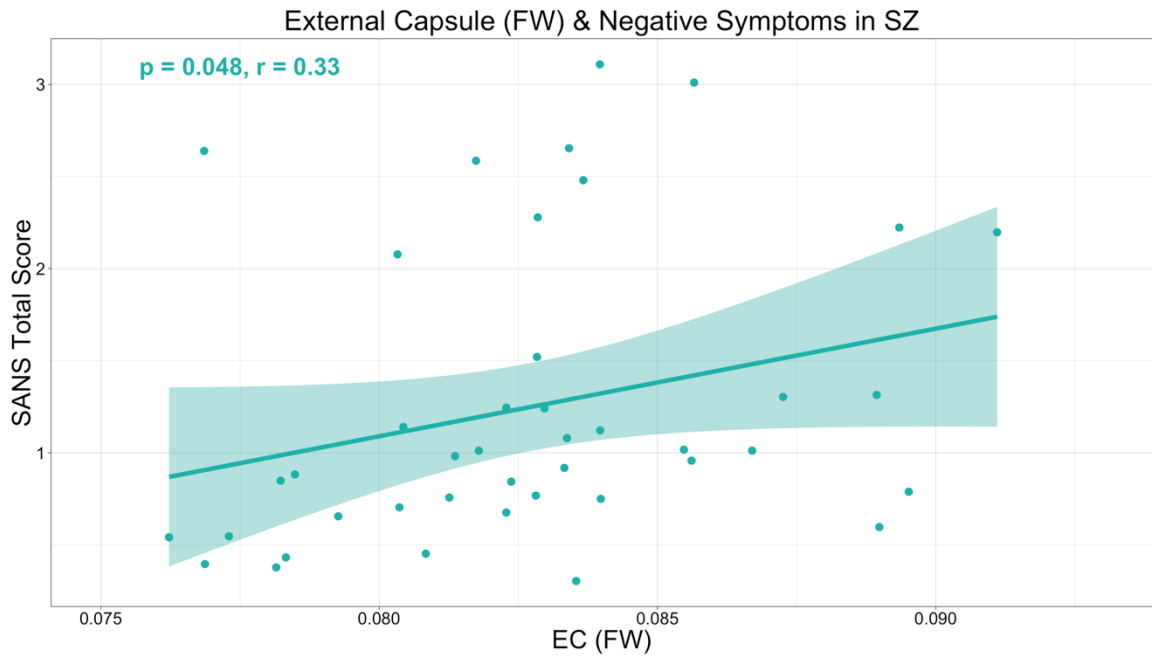


Figure 13. External Capsule (FW) & negative symptoms in SZ. The FW of the EC was positively correlated with SANS. Data was covaried for age and sex. Displaying FDR corrected p-values ($p < 0.05$).

DISCUSSION

We report WM differences in interhemispheric, thalamocortical, and limbic tracts between SZ and HC in measures of both FAt and FW. We also report FAt and FW relations between cognition and clinical symptoms in patients. Positive correlations were observed between FAt and working memory in the PCR and FXST as well as negative correlations between FW and attention/vigilance in the UNC. Positive associations between FAt and ToM were shown in average whole-brain and FXST in addition to negative associations between FW and ToM for average whole-brain and PCR. Furthermore, positive correlations between FW and negative symptoms were observed in the EC.

Microstructural Aberrations in FAt and FW

We report WM FAt aberrations and FW elevations in SZ compared to HC. Specifically, largest effects were observed for FAt reductions in the BCC, CGC, PTR, ACR, CC, and CR, all showing Cohen's d magnitudes of >0.5 (medium effect sizes). Although structural differences did not survive correction for multiple comparisons, our uncorrected FAt findings align with previous studies reporting FA reductions of the CC and CR (Ellison-Wright & Bullmore, 2009; Kubicki et al., 2007). Furthermore, a meta-analysis by the ENIGMA-DTI Working Group found significant FA reductions predominantly in frontotemporal, interhemispheric, and thalamocortical regions, with largest effects in the CC, specifically in the BCC, and in the CR (Kelly et al., 2017).

As early stages of SZ are associated with increased extracellular volume, we expected to see elevated FW for our early course patient sample. We report higher FW

values in patients compared HC, with largest effects detected for PCR, UNC, and the PTR, all showing Cohen's d magnitudes of >0.5 (medium effect sizes). While a main effect of global FW elevations for patients was observed, our uncorrected findings align with previous studies showing similar effects in first-episode patients (Lyall et al., 2017; Pasternak et al., 2012).

As FAt and FW are considered to be sensitive to illness duration, we separated early course SZ into early and later stages based on illness duration of 2 years in an attempt to detect subtle microstructural differences which may be related to the progression of SZ. Early stage SZ appeared to have significantly greater FAt in the FXST, CGH, and average whole-brain FAt compared to later stage SZ. Later stage SZ had significant reductions in the PTR, BCC, CGC, ACR, FXST, CR, and average whole-brain FAt compared to controls. For FW differences, we observed significant elevations in the FX for early stage patients compared to HC and significant elevations in the PCR in later stages compared to HC. Our findings are consistent with the studies by Pasternak et al. (2015) and Oestreich et al. (2017), both examining FAt and FW relations in chronic SZ. Pasternak et al. (2015) found FAt reductions for frontal, temporal, and occipital lobes. Oestreich et al. (2017) similarly reported significant reductions in the PTR and BCC for chronic SZ. Both studies found limited abnormal elevations in extracellular space regarding FW. For FW differences, we observed significant elevations in the FX for early stages compared to HC and significant elevations in the PCR in later stages compared to HC. The FX, however, should be interpreted with caution due to its small structure and vulnerability to partial volume effects (Pai, Soltanian-Zadeh, & Hua, 2011; Prakash & Nowinski, 2006).

Our results suggest that WM aberrations may be more prominent and widespread as illness duration progresses. Although the largest effects were observed for tracts of interhemispheric, thalamocortical, and limbic regions, the current overall findings suggest a global mechanism for WM dysconnectivity in SZ, which is thought to contribute to characteristic symptoms of schizophrenia including cognitive deficits and clinical manifestations (Kubicki et al., 2007).

Neurocognitive Correlates in FAt and FW

We report significant differences between SZ and HC for verbal learning and memory, speed of processing, social cognition, and reasoning and problem solving. These domains have been well documented as impairments in SZ (Gur et al., 2001). We further examined associations between neurocognitive domains and WM specifically in SZ and report significant correlations between WM regions and working memory and attention/vigilance. Deficits in working memory have been extensively reported in SZ (Aleman, Hijman, de Haan, & Kahn, 1999).

We report significant positive correlations between FAt of the FXST and PCR with working memory performance. FA reductions in the FX have been implicated in cognitive dysfunction and memory function in SZ (Nestor et al., 2007). The FX is a projection bundle connecting the medial temporal lobe to the hypothalamus and mamillary bodies (Catani & Thiebaut de Schotten, 2008). As our findings are in the FXST, which is a larger structure from ROI extraction, our results can be considered to be more stable than FX individually. The PCR has also been previously implicated in cognitive deficits. A recent meta-analysis

comparing mild cognitive impairment patients to HC report correlations between FA reductions in the PCR to cognitive deficits consistent with our results (Yu, Lam, & Lee, 2017). The CR is a complex bundle of projection fibers connecting the cerebral cortex to subcortical structures as well as the brainstem via the internal capsule (Catani & Thiebaut de Schotten, 2008). The CR is thought to be involved in information processing, motor functions, and higher cognitive processes (Ćurčić-Blake et al., 2015; Schmahmann & Pandya, 2008).

We also observed significant negative correlations between attention/vigilance and FW for the UNC. The UNC is an associative bundle connecting the anterior temporal lobe with the medial and lateral orbitofrontal cortex with both the frontal and temporal lobes (Catani & Thiebaut de Schotten, 2008) and is thought to be involved in various cognitive functioning including attention, emotion processing, memory, and language functions (Gaffan & Wilson, 2008; Ross, 2008; Singh et al., 2016). Our FW findings converge with a study by Singh et al. (2016) reporting associations between FA of the UNC and attention. However, we must also note that our study is the first to implicate a role for FW in cognitive deficits of early-course patients.

Sociocognitive Correlates in FAt and FW

Social cognitive impairments are considered to be core feature of SZ and is further demonstrated in our sample by the lower scores for patients compared to HC on the social cognition domain of the MATRICS. We found significant associations between WM regions and social cognition factors. Previous studies have shown associations between the

frontal cortex and thalamic regions and social functioning (Andreasen, 1997; Andreasen et al., 1999; Koshiyama et al., 2018; Miyata et al., 2010). The CR contains reciprocal connections from the thalamus to the cerebral cortex and has been shown to be involved in information processing and may potentially contribute to social and emotional functioning (Catani & Thiebaut de Schotten, 2008).

To our knowledge, we report the first FAt and FW findings suggesting potential neural correlates of social cognition. We report significant associations in WM regions with the ToM social cognition factor. ToM has been shown to be related to lower severity in clinical symptomatology and associated with subjective quality of life (Maat, Fett, & Derks, 2012). Past research has shown that the medial and orbitofrontal cortices play major roles in ToM (Baron-Cohen et al., 1994; Fletcher et al., 1995). Scores in the other two factors failed to show any significant association with FAt and FW measures.

We report significant positive correlations between higher FAt of the FXST and average whole-brain FAt with ToM. The FX is involved in the limbic system and specifically in the amygdala circuitry. The amygdala is also known to play a major role in social cognition and ToM (Michael F. Green, Horan, & Lee, 2015). We also report significant negative correlations between average whole-brain FW and the PCR. Koshiyama et al. (2018) found significant associations between FA of the ACR and social cognition, however, we report associations in the FAt of the PCR. As relations between WM and social cognition have been relatively unexplored, future studies are necessary to address inconsistent findings.

Clinical Correlates in FAt and FW

We also investigated possible associations between clinical symptoms in SZ and WM integrity. Although we report no significant associations between FAt and FW for positive symptoms, we found a positive association between FAt reductions in WM of the EC with greater severity of negative symptoms. Negative symptoms in SZ are shown to be related to deficits in WM regions (Nestor et al., 2008; Skelly et al., 2008) as well as lower FA values (Mitelman et al., 2006; Sigmundsson et al., 2001; Viher et al., 2016). Viher et al. (2016) correspondingly reported associations between reduced FA in the EC with greater negative symptoms. The EC projects from the cortex to the basal ganglia, specifically to the striatum (Catani & Thiebaut de Schotten, 2008). Disrupted integrity in the EC constitute underlying pathologies which may lead to specific clinical symptomology present in schizophrenia.

Furthermore, no significant effects of illness duration or medication dosage were identified in our study. Many cross-sectional DTI studies have also reported no detectable correlations between FA and medication (Samartzis et al., 2014).

Implication of Findings

We must note that our study is the first to implicate a role for FW in cognitive deficits of early-course patients. Lyall et al. (2017) previously demonstrated that elevated FW for first episode psychosis patients had a positive relationship with neurocognitive functioning after 12 weeks of antipsychotic treatment. To our knowledge, our study is also the first to examine FW in relation to social cognition and clinical symptoms. As FW is

considered to be an indirect measure of neuroinflammatory response during early stages of SZ, it is critical to detect biological markers prior to the onset of clinically detectable symptoms. The potential FW neural correlates that we identified in the current study may be used as biomarkers for CRT to predict better functional outcome and response to SZ treatment.

Limitations

Some limitations of this study must be addressed. Although TBSS is widely used for WM analysis, this method has some limitations. TBSS reduces WM tracts into a skeleton and projects only the highest FA value along the projection often resulting in misregistration causing potential loss of information (Zalesky, 2011) and susceptibility to artifacts (Schwarz et al., 2014). Limitations also include partial volume effects, skeleton shapes, image noise level, and registration errors (Bach et al., 2014). Additionally, smaller tracts, such as the FX, are more susceptible to misalignment (Nestor et al., 2007). Although FA values are thought to represent the coherence of WM as well as the microstructural properties of axons including axon diameter, degree of myelination, and fiber packing density (Mukherjee, Berman, Chung, Hess, & Henry, 2008). It is furthermore important to also examine other diffusion indices such as AD, MD, and RD in SZ in order to attain a more complete understanding of how microstructural integrity influences the disrupted neural networks in SZ.

We also acknowledge that our FAt and FW results must be interpreted with caution as FWI is a novel method. FW is considered to be an indirect measure of extracellular

fractional volume and should only be considered as a proxy for neuroinflammation (Pasternak et al., 2015). Analyses and consideration of other diffusivity measures may assist in identification of other potential underlying biological pathologies contributing to the present findings. Such pathologies may include reduced neuronal size (Rajkowska, Selemon, & Goldman-Rakic, 1998) which may be contributing to FAt reductions as well as atrophy caused by excessive synaptic pruning contributing to elevated FW results (Boksa, 2012). As we present the utilization of novel imaging methods, this research must be replicated in larger sample sizes in order to validate our exploratory analysis using FAt and FW measures.

Our use of specific social cognition factors must also be addressed as a potential limitation. The three factors of social cognition were derived specifically from analyses of a larger subset of the present sample and potentially may only address social cognitive impairments tailored to the present sample. We must note that these factors may not be applicable to a broader population of SZ.

Although the SZ and HC samples did not significantly differ, the smaller HC sample size may modulate the degree of WM microstructural changes detected due to power reduction. Whole-brain imaging studies with larger sample sizes are required to elucidate the associations between WM integrity and cognitive correlates. As early course SZ includes a wide range for illness duration (<8 years), the heterogeneity in our study may be preventing the prospect of detecting subtle WM microstructural changes. Age and stage of illness have been shown to effect WM patterns of brain changes (Ellison-Wright & Bullmore, 2009; Jones et al., 2006). An additional consideration to take in to account is

that all patients were medicated and relatively stable, hence our results may not be applicable to a broad SZ population. However, an exploratory correlation analysis indicated no significant associations between FAt and FW with medication, duration of illness, and age of onset in our main findings.

Furthermore, due to the cross-sectional design of this analyses, we are unable to draw definitive conclusions about the underlying neural correlates observed in cognitive and clinical outcomes in SZ. We are also unable to state whether relationships between WM integrity and neurocognitive impairment and social dysfunction is causal.

Future Directions

We report baseline results from a longitudinal study focusing on CET. Future work in this sample will investigate the association between of CET and WM microstructural changes in addition to identifying potential improvements in neurocognitive and social cognitive domains as well as in clinical symptoms. Additionally, as we report correlations between WM and cognitive and clinical measures, we further aim to assess whether these correlates can be considered as potential biomarkers for predicting sensitivity and improvements to CET in the longitudinal dataset. Furthermore, future investigations on the longitudinal effects of CET post-treatment are warranted in order to assess durability as well as the long-term effects CET has on brain structure and function in SZ.

Conclusion

In conclusion, this study investigated WM microstructural differences in early course SZ in comparison to HC using measures of FAt and FW in ROIs across the whole brain. We further examined associations between WM and measures of cognition and clinical symptomatology. We report disrupted WM microstructure in SZ, specifically reductions in FAt ROIs along with elevated FW ROIs. To our knowledge, this is the first study to report findings for both FAt and FW neural correlates in neurocognition, social cognition, and negative symptoms for early course SZ. We hope our findings will contribute to a greater understanding of the neural networks underlying early course SZ symptomatology as changes in WM integrity may be a fundamental pathophysiological mechanism underlying clinical presentation of SZ before the manifestation of clinical symptoms.

APPENDIX

Supplemental Table 1: The effect sizes for FAt differences between SZ and HC. Data was covaried for age and sex. * indicates $p < 0.05$.

Region	p-value	Cohen's d	CI-Lower	CI-Upper	FDR p-value
ACR	0.023	-0.631	-1.165	-0.092	0.14
ALIC	0.141	-0.393	-0.921	0.138	0.294
AverageFAt	0.077	-0.476	-1.006	0.057	0.214
BCC	0.008*	-0.741	-1.279	-0.198	0.108
CC	0.028*	-0.614	-1.147	-0.076	0.14
CGC	0.009*	-0.691	-1.227	-0.15	0.108
CGH	0.391	-0.232	-0.758	0.295	0.543
CR	0.043*	-0.542	-1.073	-0.007	0.179
CST	0.679	0.112	-0.414	0.637	0.738
EC	0.818	-0.057	-0.582	0.468	0.818
FX	0.376	-0.245	-0.771	0.283	0.543
FXST	0.127	-0.427	-0.955	0.105	0.289
GCC	0.072	-0.503	-1.033	0.031	0.214
IC	0.226	-0.315	-0.842	0.214	0.353
IFO	0.467	0.188	-0.339	0.713	0.614
PCR	0.575	-0.149	-0.674	0.377	0.685
PLIC	0.816	-0.062	-0.587	0.463	0.818
PTR	0.013*	-0.709	-1.245	-0.167	0.108
RLIC	0.172	-0.353	-0.88	0.177	0.331
SCC	0.491	-0.195	-0.72	0.332	0.614
SCR	0.116	-0.423	-0.951	0.109	0.289
SFO	0.209	-0.332	-0.859	0.197	0.348
SLF	0.192	-0.34	-0.867	0.19	0.343
SS	0.069	-0.506	-1.036	0.028	0.214
UNC	0.615	-0.135	-0.66	0.391	0.699

Supplemental Table 2: The effect sizes for FW differences between SZ and HC. Data was covaried for age and sex. * indicates $p < 0.05$.

Region	p-value	Cohen's d	CI-Lower	CI-Upper	FDR p-value
ACR	0.526	0.189	-0.338	0.714	0.758
ALIC	0.961	-0.013	-0.538	0.512	0.961
AverageFW	0.066	0.527	-0.008	1.058	0.219
BCC	0.848	0.054	-0.471	0.579	0.922
CC	0.546	0.168	-0.358	0.693	0.758
CGC	0.061	0.55	0.014	1.081	0.219
CGH	0.901	-0.034	-0.559	0.491	0.939
CR	0.759	0.086	-0.44	0.611	0.886
CST	0.78	0.079	-0.446	0.604	0.886
EC	0.166	-0.386	-0.914	0.145	0.377
FX	0.057	0.506	-0.028	1.036	0.219
FXST	0.721	0.104	-0.422	0.629	0.886
GCC	0.422	0.21	-0.317	0.735	0.703
IC	0.34	0.253	-0.275	0.779	0.663
IFO	0.491	0.186	-0.341	0.711	0.758
PCR	0.012*	0.684	0.143	1.22	0.219
PLIC	0.634	-0.13	-0.655	0.396	0.834
PTR	0.039*	0.579	0.042	1.111	0.219
RLIC	0.08	0.501	-0.033	1.031	0.222
SCC	0.404	0.225	-0.302	0.751	0.703
SCR	0.057	-0.504	-1.034	0.03	0.219
SFO	0.345	0.258	-0.27	0.784	0.663
SLF	0.14	-0.422	-0.95	0.11	0.35
SS	0.07	0.492	-0.042	1.022	0.219
UNC	0.036*	0.602	0.065	1.135	0.219

Supplemental Table 3: The effect sizes for FAt differences between SZ stages and HC. Data was covaried for age and sex. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

Region	Early Stage SZ vs HC		Early Stage SZ vs Late Stage SZ		Late Stage SZ vs HC	
	p-value	Cohen's d	p-value	Cohen's d	p-value	Cohen's d
ACR	0.370	-0.395	0.405	0.247	0.049*	-0.738
ALIC	0.507	-0.291	0.841	0.057	0.449	-0.446
Average FAt	0.908	0.014	0.043*	0.720	0.043*	-0.696
BCC	0.120	-0.692	0.720	0.114	0.029*	-0.755
CC	0.245	-0.533	0.704	0.119	0.087	-0.641
CGC	0.154	-0.561	0.620	0.164	0.028*	-0.742
CGH	0.236	0.354	0.020*	0.864	0.114	-0.509
CR	0.627	-0.179	0.172	0.510	0.045*	-0.705
CST	0.780	0.270	0.780	0.210	0.865	0.052
EC	0.675	0.130	0.675	0.325	0.675	-0.133
FX	0.648	-0.341	0.648	-0.142	0.648	-0.203
FXST	0.397	0.272	0.008*	0.979	0.017*	-0.731
GCC	0.448	-0.393	0.647	0.141	0.200	-0.543
IC	0.725	-0.213	0.767	0.089	0.656	-0.366
IFO	0.257	0.517	0.257	0.506	0.821	0.068
PCR	0.283	0.399	0.080	0.837	0.283	-0.337
PLIC	0.908	-0.163	0.908	-0.160	0.965	-0.016
PTR	0.452	-0.321	0.123	0.561	0.010*	-0.862
RLIC	0.844	-0.083	0.323	0.445	0.267	-0.459
SCC	0.860	-0.152	0.860	0.053	0.860	-0.210
SCR	0.900	-0.059	0.169	0.503	0.130	-0.587
SFO	0.682	-0.267	0.781	0.092	0.615	-0.355
SLF	0.867	0.041	0.128	0.637	0.128	-0.484
SS	0.886	-0.084	0.095	0.636	0.056*	-0.661
UNC	0.318	0.342	0.123	0.694	0.318	-0.321

Supplemental Table 4: The effect sizes for FW differences between SZ stages and HC. Data was covaried for age and sex. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

Region	Early Stage SZ vs HC		Early Stage SZ vs Late Stage SZ		Late Stage SZ vs Healthy Controls	
	p-value	Cohen's d	p-value	Cohen's d	p-value	Cohen's d
ACR	0.519	-0.323	0.286	-0.539	0.286	-0.539
ALIC	0.849	-0.179	0.849	-0.246	0.849	-0.246
Average FW	0.424	0.382	0.653	-0.129	0.653	-0.129
BCC	0.993	0.061	0.993	0.003	0.993	0.003
CC	0.817	0.122	0.817	-0.074	0.817	-0.074
CGC	0.473	0.309	0.473	-0.191	0.473	-0.191
CGH	0.825	-0.220	0.825	-0.245	0.825	-0.245
CR	0.332	-0.472	0.144	-0.675	0.144	-0.675
CST	0.938	0.028	0.938	-0.054	0.938	-0.054
EC	0.268	-0.545	0.333	-0.294	0.333	-0.294
FX	0.017	1.002	0.064	0.727	0.064	0.727
FXST	0.809	0.134	0.809	0.071	0.809	0.071
GCC	0.805	0.098	0.805	-0.185	0.805	-0.185
IC	0.842	-0.050	0.260	-0.429	0.260	-0.429
IFO	0.292	-0.384	0.059	-0.829	0.059	-0.829
PCR	0.281	0.463	0.371	-0.288	0.371	-0.288
PLIC	0.361	-0.477	0.361	-0.423	0.361	-0.423
PTR	0.182	0.617	0.985	0.009	0.985	0.009
RLIC	0.501	0.223	0.501	-0.264	0.501	-0.264
SCC	0.782	0.176	0.782	-0.094	0.782	-0.094
SCR	0.103	-0.752	0.287	-0.373	0.287	-0.373
SFO	0.680	0.344	0.692	0.126	0.692	0.126
SLF	0.350	-0.543	0.882	-0.050	0.882	-0.050
SS	0.516	0.307	0.516	-0.194	0.516	-0.194
UNC	0.163	0.635	0.952	0.021	0.952	0.021

Supplemental Table 5: The effect sizes for neurocognitive differences between SZ and HC. Data was covaried for age, sex, race, and education. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

Region	p-value	Cohen's d	CI-Lower	CI-Upper	FDR p-value
AV	0.386	-0.237	-0.763	0.290	0.450
RPS	0.040	-0.566	-1.098	-0.030	0.070
SC	0.005	-0.718	-1.255	-0.176	0.018
SOP	0.009	-0.673	-1.208	-0.133	0.021
VLBVM	0.246	0.316	-0.213	0.843	0.344
VLHVL	0.004	-0.772	-1.311	-0.228	0.018
WM	0.514	-0.167	-0.692	0.359	0.514

Supplemental Table 6: Correlations between FAt ROIs and neurocognitive domains. Data was covaried for age, sex, race, and education. AV= attention/vigilance; RPS= reasoning and problem solving; SC= social cognition; VLBVM= visual learning & memory; VLHVL= verbal learning & memory; WM= working memory. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

ROI-Neurocognition	r value	p-value	FDR p-value
ACR-AV	0.021	0.890	0.890
ACR-RPS	0.084	0.584	0.890
ACR-SC	-0.028	0.853	0.890
ACR-SOP	0.126	0.403	0.890
ACR-VLBVM	0.022	0.886	0.890
ACR-VLHVL	0.047	0.754	0.890
ACR-WM	0.022	0.882	0.890
ALIC-AV	0.111	0.462	0.845
ALIC-RPS	-0.083	0.585	0.845
ALIC-SC	0.154	0.307	0.845
ALIC-SOP	-0.074	0.623	0.845
ALIC-VLBVM	-0.007	0.962	0.962
ALIC-VLHVL	0.053	0.725	0.845
ALIC-WM	0.071	0.639	0.845
AverageFAt-AV	-0.020	0.896	0.896
AverageFAt-RPS	0.051	0.738	0.896
AverageFAt-SC	0.118	0.433	0.758
AverageFAt-SOP	0.138	0.359	0.758

AverageFAt-VLBVM	0.133	0.377	0.758
AverageFAt-VLHVL	0.037	0.808	0.896
AverageFAt-WM	0.253	0.089	0.626
BCC-AV	0.199	0.185	0.324
BCC-RPS	0.238	0.115	0.269
BCC-SC	-0.003	0.982	0.982
BCC-SOP	0.256	0.086	0.269
BCC-VLBVM	0.112	0.458	0.610
BCC-VLHVL	0.096	0.523	0.610
BCC-WM	0.256	0.086	0.269
CC-AV	0.121	0.423	0.493
CC-RPS	0.237	0.116	0.493
CC-SC	0.059	0.698	0.698
CC-SOP	0.168	0.264	0.493
CC-VLBVM	0.146	0.333	0.493
CC-VLHVL	0.140	0.352	0.493
CC-WM	0.214	0.152	0.493
CGC-AV	-0.237	0.113	0.792
CGC-RPS	0.083	0.585	0.810
CGC-SC	0.036	0.810	0.810
CGC-SOP	0.083	0.584	0.810
CGC-VLBVM	-0.076	0.616	0.810
CGC-VLHVL	0.039	0.798	0.810
CGC-WM	-0.148	0.327	0.810
CGH-AV	0.090	0.551	0.965
CGH-RPS	-0.204	0.178	0.524
CGH-SC	0.182	0.224	0.524
CGH-SOP	-0.003	0.986	0.986
CGH-VLBVM	0.027	0.857	0.986
CGH-VLHVL	-0.032	0.834	0.986
CGH-WM	0.296	0.046	0.321
CR-AV	0.014	0.924	0.936
CR-RPS	0.084	0.582	0.936
CR-SC	0.071	0.636	0.936
CR-SOP	0.147	0.329	0.936
CR-VLBVM	0.046	0.760	0.936
CR-VLHVL	0.012	0.936	0.936
CR-WM	0.187	0.212	0.936

CST-AV	-0.234	0.117	0.250
CST-RPS	-0.233	0.123	0.250
CST-SC	-0.046	0.760	0.887
CST-SOP	-0.219	0.143	0.250
CST-VLBVM	-0.123	0.415	0.580
CST-VLHVL	-0.260	0.082	0.250
CST-WM	0.017	0.909	0.909
EC-AV	0.017	0.909	1.000
EC-RPS	0.062	0.684	1.000
EC-SC	0.194	0.196	1.000
EC-SOP	0.050	0.740	1.000
EC-VLBVM	0.097	0.522	1.000
EC-VLHVL	0.000	1.000	1.000
EC-WM	0.140	0.353	1.000
FX-AV	0.094	0.534	0.813
FX-RPS	0.162	0.287	0.813
FX-SC	-0.260	0.081	0.568
FX-SOP	0.070	0.642	0.813
FX-VLBVM	-0.056	0.713	0.813
FX-VLHVL	0.049	0.747	0.813
FX-WM	-0.036	0.813	0.813
FXST-AV	-0.110	0.467	0.788
FXST-RPS	-0.164	0.282	0.788
FXST-SC	0.096	0.526	0.788
FXST-SOP	0.062	0.680	0.788
FXST-VLBVM	0.041	0.788	0.788
FXST-VLHVL	0.053	0.726	0.788
FXST-WM	0.395	0.007	0.048*
GCC-AV	-0.144	0.338	0.973
GCC-RPS	0.131	0.388	0.973
GCC-SC	-0.005	0.973	0.973
GCC-SOP	-0.077	0.612	0.973
GCC-VLBVM	0.007	0.964	0.973
GCC-VLHVL	0.068	0.652	0.973
GCC-WM	0.046	0.760	0.973
IC-AV	0.098	0.515	0.948
IC-RPS	-0.046	0.762	0.948
IC-SC	0.135	0.372	0.948

IC-SOP	-0.024	0.874	0.948
IC-VLBVM	0.050	0.739	0.948
IC-VLHVL	0.010	0.948	0.948
IC-WM	0.138	0.360	0.948
IFO-AV	-0.035	0.816	0.816
IFO-RPS	0.150	0.325	0.569
IFO-SC	0.258	0.084	0.294
IFO-SOP	0.099	0.512	0.597
IFO-VLBVM	0.266	0.075	0.294
IFO-VLHVL	0.177	0.238	0.555
IFO-WM	0.119	0.430	0.597
PCR-AV	0.084	0.578	0.578
PCR-RPS	0.105	0.493	0.578
PCR-SC	0.095	0.528	0.578
PCR-SOP	0.240	0.108	0.379
PCR-VLBVM	0.182	0.226	0.527
PCR-VLHVL	0.144	0.338	0.578
PCR-WM	0.463	0.001	0.010*
PLIC-AV	0.182	0.226	0.998
PLIC-RPS	0.010	0.948	0.998
PLIC-SC	0.081	0.592	0.998
PLIC-SOP	-0.129	0.392	0.998
PLIC-VLBVM	0.000	0.998	0.998
PLIC-VLHVL	-0.004	0.978	0.998
PLIC-WM	0.051	0.736	0.998
PTR-AV	0.106	0.481	0.674
PTR-RPS	0.053	0.728	0.849
PTR-SC	0.178	0.236	0.498
PTR-SOP	0.181	0.227	0.498
PTR-VLBVM	0.161	0.284	0.498
PTR-VLHVL	-0.003	0.983	0.983
PTR-WM	0.243	0.103	0.498
RLIC-AV	-0.003	0.986	0.986
RLIC-RPS	-0.061	0.688	0.964
RLIC-SC	0.151	0.317	0.739
RLIC-SOP	0.173	0.250	0.739
RLIC-VLBVM	0.172	0.251	0.739
RLIC-VLHVL	-0.027	0.859	0.986

RLIC-WM	0.070	0.642	0.964
SCC-AV	0.125	0.408	0.692
SCC-RPS	0.174	0.253	0.590
SCC-SC	0.174	0.245	0.590
SCC-SOP	0.062	0.682	0.692
SCC-VLBVM	0.231	0.122	0.590
SCC-VLHVL	0.060	0.692	0.692
SCC-WM	0.062	0.680	0.692
SCR-AV	-0.025	0.866	0.984
SCR-RPS	0.037	0.809	0.984
SCR-SC	0.159	0.290	0.984
SCR-SOP	0.107	0.477	0.984
SCR-VLBVM	0.009	0.951	0.984
SCR-VLHVL	0.003	0.984	0.984
SCR-WM	0.282	0.058	0.405
SFO-AV	0.085	0.575	0.960
SFO-RPS	-0.008	0.960	0.960
SFO-SC	0.018	0.903	0.960
SFO-SOP	0.013	0.934	0.960
SFO-VLBVM	-0.109	0.471	0.960
SFO-VLHVL	-0.040	0.794	0.960
SFO-WM	0.175	0.243	0.960
SLF-AV	-0.001	0.995	0.995
SLF-RPS	0.076	0.617	0.912
SLF-SC	0.068	0.652	0.912
SLF-SOP	0.126	0.405	0.912
SLF-VLBVM	0.097	0.521	0.912
SLF-VLHVL	-0.003	0.983	0.995
SLF-WM	0.160	0.289	0.912
SS-AV	0.101	0.503	0.586
SS-RPS	0.044	0.772	0.772
SS-SC	0.102	0.500	0.586
SS-SOP	0.181	0.229	0.586
SS-VLBVM	0.107	0.479	0.586
SS-VLHVL	-0.162	0.280	0.586
SS-WM	0.179	0.232	0.586
UNC-AV	-0.016	0.918	0.918
UNC-RPS	0.024	0.874	0.918

UNC-SC	0.124	0.410	0.918
UNC-SOP	-0.199	0.183	0.918
UNC-VLBVM	-0.041	0.784	0.918
UNC-VLHVL	-0.115	0.445	0.918
UNC-WM	0.067	0.656	0.918

Supplemental Table 7: Correlations between FW ROIs and neurocognitive domains. Data was covaried for age, sex, race, and education. AV= attention/vigilance; RPS= reasoning and problem solving; SC= social cognition; VLBVM= visual learning & memory; VLHVL= verbal learning & memory; WM= working memory. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

ROI-Neurocognition	r value	p-value	FDR p-value
ACR-AV	0.048	0.753	0.852
ACR-RPS	-0.029	0.852	0.852
ACR-SC	0.034	0.823	0.852
ACR-SOP	-0.085	0.574	0.852
ACR-VLBVM	-0.123	0.415	0.852
ACR-VLHVL	-0.065	0.665	0.852
ACR-WM	-0.157	0.297	0.852
ALIC-AV	-0.135	0.371	0.694
ALIC-RPS	0.120	0.432	0.694
ALIC-SC	0.059	0.694	0.694
ALIC-SOP	0.075	0.620	0.694
ALIC-VLBVM	-0.074	0.624	0.694
ALIC-VLHVL	-0.099	0.510	0.694
ALIC-WM	-0.161	0.286	0.694
AverageFW-AV	-0.034	0.822	0.936
AverageFW-RPS	0.046	0.764	0.936
AverageFW-SC	0.106	0.481	0.936
AverageFW-SOP	0.080	0.594	0.936
AverageFW-VLBVM	0.012	0.936	0.936
AverageFW-VLHVL	0.023	0.881	0.936
AverageFW-WM	-0.110	0.465	0.936
BCC-AV	-0.195	0.194	0.944
BCC-RPS	-0.002	0.989	1.000
BCC-SC	0.166	0.270	0.944
BCC-SOP	-0.032	0.835	1.000

BCC-VLBVM	0.000	1.000	1.000
BCC-VLHVL	-0.046	0.761	1.000
BCC-WM	-0.123	0.414	0.966
CC-AV	-0.127	0.399	0.882
CC-RPS	0.023	0.882	0.882
CC-SC	0.186	0.216	0.882
CC-SOP	-0.042	0.783	0.882
CC-VLBVM	-0.028	0.854	0.882
CC-VLHVL	-0.044	0.769	0.882
CC-WM	-0.103	0.494	0.882
CGC-AV	0.000	0.999	0.999
CGC-RPS	0.203	0.180	0.629
CGC-SC	0.202	0.179	0.629
CGC-SOP	-0.031	0.839	0.999
CGC-VLBVM	0.104	0.490	0.999
CGC-VLHVL	-0.001	0.995	0.999
CGC-WM	0.016	0.914	0.999
CGH-AV	-0.012	0.939	0.939
CGH-RPS	-0.168	0.268	0.469
CGH-SC	-0.025	0.868	0.939
CGH-SOP	-0.111	0.460	0.644
CGH-VLBVM	-0.282	0.058	0.202
CGH-VLHVL	-0.200	0.182	0.424
CGH-WM	-0.344	0.020	0.137
CR-AV	0.044	0.773	0.982
CR-RPS	0.004	0.982	0.982
CR-SC	0.013	0.933	0.982
CR-SOP	-0.068	0.651	0.982
CR-VLBVM	-0.131	0.383	0.982
CR-VLHVL	-0.058	0.703	0.982
CR-WM	-0.230	0.124	0.871
CST-AV	-0.138	0.360	0.504
CST-RPS	0.216	0.154	0.504
CST-SC	0.118	0.434	0.506
CST-SOP	0.063	0.677	0.677
CST-VLBVM	0.198	0.186	0.504
CST-VLHVL	0.171	0.254	0.504
CST-WM	-0.142	0.344	0.504

EC-AV	0.060	0.690	0.968
EC-RPS	0.101	0.510	0.968
EC-SC	0.001	0.993	0.993
EC-SOP	0.088	0.557	0.968
EC-VLBVM	0.138	0.359	0.968
EC-VLHVL	-0.024	0.876	0.993
EC-WM	-0.060	0.692	0.968
FX-AV	-0.267	0.073	0.255
FX-RPS	-0.237	0.116	0.271
FX-SC	0.284	0.056	0.255
FX-SOP	-0.070	0.644	0.871
FX-VLBVM	-0.031	0.836	0.871
FX-VLHVL	0.025	0.871	0.871
FX-WM	-0.127	0.398	0.696
FXST-AV	-0.042	0.783	0.890
FXST-RPS	0.127	0.404	0.890
FXST-SC	-0.021	0.890	0.890
FXST-SOP	-0.045	0.764	0.890
FXST-VLBVM	-0.124	0.410	0.890
FXST-VLHVL	-0.082	0.585	0.890
FXST-WM	-0.151	0.316	0.890
GCC-AV	-0.088	0.560	0.978
GCC-RPS	-0.004	0.978	0.978
GCC-SC	0.180	0.229	0.978
GCC-SOP	-0.050	0.739	0.978
GCC-VLBVM	-0.110	0.464	0.978
GCC-VLHVL	0.010	0.950	0.978
GCC-WM	-0.067	0.658	0.978
IC-AV	-0.046	0.759	0.852
IC-RPS	0.109	0.474	0.852
IC-SC	0.179	0.232	0.812
IC-SOP	-0.066	0.664	0.852
IC-VLBVM	-0.078	0.605	0.852
IC-VLHVL	-0.028	0.852	0.852
IC-WM	-0.280	0.059	0.416
IFO-AV	0.105	0.487	0.798
IFO-RPS	-0.005	0.973	0.973
IFO-SC	-0.107	0.479	0.798

IFO-SOP	-0.048	0.751	0.876
IFO-VLBVM	-0.086	0.570	0.798
IFO-VLHVL	-0.099	0.509	0.798
IFO-WM	-0.177	0.238	0.798
PCR-AV	-0.041	0.784	0.915
PCR-RPS	0.135	0.376	0.878
PCR-SC	0.048	0.752	0.915
PCR-SOP	0.016	0.915	0.915
PCR-VLBVM	0.176	0.240	0.878
PCR-VLHVL	0.138	0.358	0.878
PCR-WM	-0.052	0.733	0.915
PLIC-AV	-0.018	0.906	1.000
PLIC-RPS	0.000	0.999	1.000
PLIC-SC	0.000	1.000	1.000
PLIC-SOP	-0.098	0.517	0.905
PLIC-VLBVM	-0.234	0.118	0.324
PLIC-VLHVL	-0.221	0.139	0.324
PLIC-WM	-0.341	0.021	0.147
PTR-AV	-0.014	0.927	0.927
PTR-RPS	0.153	0.314	0.578
PTR-SC	0.105	0.488	0.578
PTR-SOP	0.103	0.495	0.578
PTR-VLBVM	0.144	0.340	0.578
PTR-VLHVL	0.257	0.085	0.578
PTR-WM	0.115	0.444	0.578
RLIC-AV	-0.020	0.897	0.948
RLIC-RPS	0.077	0.614	0.948
RLIC-SC	0.226	0.131	0.918
RLIC-SOP	-0.010	0.948	0.948
RLIC-VLBVM	0.014	0.928	0.948
RLIC-VLHVL	0.154	0.306	0.948
RLIC-WM	-0.084	0.580	0.948
SCC-AV	-0.100	0.509	0.885
SCC-RPS	0.031	0.840	0.885
SCC-SC	0.146	0.332	0.885
SCC-SOP	-0.062	0.680	0.885
SCC-VLBVM	0.024	0.875	0.885
SCC-VLHVL	-0.022	0.885	0.885

SCC-WM	-0.114	0.449	0.885
SCR-AV	0.064	0.671	0.860
SCR-RPS	-0.106	0.486	0.850
SCR-SC	-0.046	0.763	0.860
SCR-SOP	0.027	0.860	0.860
SCR-VLBVM	-0.282	0.058	0.405
SCR-VLHVL	-0.170	0.259	0.604
SCR-WM	-0.206	0.168	0.589
SFO-AV	-0.144	0.339	0.990
SFO-RPS	-0.037	0.808	0.990
SFO-SC	-0.010	0.947	0.990
SFO-SOP	0.002	0.990	0.990
SFO-VLBVM	-0.181	0.228	0.990
SFO-VLHVL	-0.018	0.904	0.990
SFO-WM	0.003	0.983	0.990
SLF-AV	-0.028	0.852	0.852
SLF-RPS	-0.289	0.055	0.385
SLF-SC	0.108	0.473	0.827
SLF-SOP	0.060	0.691	0.852
SLF-VLBVM	0.029	0.847	0.852
SLF-VLHVL	0.205	0.170	0.596
SLF-WM	0.125	0.405	0.827
SS-AV	-0.013	0.931	0.931
SS-RPS	0.020	0.896	0.931
SS-SC	-0.033	0.827	0.931
SS-SOP	-0.113	0.452	0.931
SS-VLBVM	0.113	0.455	0.931
SS-VLHVL	0.071	0.637	0.931
SS-WM	-0.044	0.772	0.931
UNC-AV	-0.419	0.004	0.028*
UNC-RPS	-0.108	0.481	0.673
UNC-SC	0.199	0.185	0.557
UNC-SOP	-0.176	0.242	0.557
UNC-VLBVM	0.037	0.807	0.807
UNC-VLHVL	0.150	0.318	0.557
UNC-WM	-0.081	0.592	0.691

Supplemental Table 8: Correlations between FAt ROIs and social cognitive domains. Data was covaried for age, sex, and race. F1_MESCEIT= Emotion Management; F2_TOM= Theory of Mind; F3_ER= Emotion Perception. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

ROI-Social Cognition	r value	p-value	FDR p-value
ACR-F1_MSCEIT	0.041	0.799	0.799
ACR-F2_TOM	0.194	0.229	0.601
ACR-F3_ER	0.136	0.401	0.601
ALIC-F1_MSCEIT	0.120	0.458	0.458
ALIC-F2_TOM	0.304	0.057	0.172
ALIC-F3_ER	0.144	0.372	0.458
AverageFAt-F1_MSCEIT	0.103	0.527	0.527
AverageFAt-F2_TOM	0.457	0.003	0.010*
AverageFAt-F3_ER	0.138	0.396	0.527
BCC-F1_MSCEIT	0.124	0.446	0.669
BCC-F2_TOM	0.166	0.304	0.669
BCC-F3_ER	0.035	0.829	0.829
CC-F1_MSCEIT	0.118	0.467	0.593
CC-F2_TOM	0.174	0.283	0.593
CC-F3_ER	0.087	0.593	0.593
CGC-F1_MSCEIT	-0.007	0.966	0.966
CGC-F2_TOM	0.091	0.575	0.966
CGC-F3_ER	-0.053	0.742	0.966
CGH-F1_MSCEIT	0.043	0.793	0.793
CGH-F2_TOM	0.208	0.196	0.469
CGH-F3_ER	-0.163	0.312	0.469
CR-F1_MSCEIT	0.059	0.715	0.715
CR-F2_TOM	0.307	0.054	0.163
CR-F3_ER	0.064	0.695	0.715
CST-F1_MSCEIT	-0.146	0.366	0.366
CST-F2_TOM	0.230	0.153	0.366
CST-F3_ER	-0.162	0.315	0.366
EC-F1_MSCEIT	0.188	0.244	0.366
EC-F2_TOM	0.308	0.054	0.162
EC-F3_ER	0.072	0.656	0.656
FX-F1_MSCEIT	-0.111	0.496	0.744
FX-F2_TOM	0.114	0.483	0.744

FX-F3_ER	-0.047	0.771	0.771
FXST-F1_MSCEIT	0.199	0.218	0.327
FXST-F2_TOM	0.486	0.002	0.005*
FXST-F3_ER	-0.011	0.948	0.948
GCC-F1_MSCEIT	0.088	0.586	0.586
GCC-F2_TOM	0.206	0.202	0.396
GCC-F3_ER	0.180	0.264	0.396
IC-F1_MSCEIT	-0.018	0.914	0.988
IC-F2_TOM	0.356	0.025	0.074
IC-F3_ER	-0.003	0.988	0.988
IFO-F1_MSCEIT	0.129	0.427	0.641
IFO-F2_TOM	0.262	0.102	0.307
IFO-F3_ER	-0.063	0.697	0.697
PCR-F1_MSCEIT	-0.043	0.791	0.791
PCR-F2_TOM	0.263	0.101	0.303
PCR-F3_ER	-0.051	0.754	0.791
PLIC-F1_MSCEIT	-0.188	0.244	0.363
PLIC-F2_TOM	0.321	0.044	0.132
PLIC-F3_ER	-0.147	0.363	0.363
PTR-F1_MSCEIT	0.176	0.276	0.829
PTR-F2_TOM	0.079	0.626	0.833
PTR-F3_ER	0.034	0.833	0.833
RLIC-F1_MSCEIT	0.128	0.429	0.643
RLIC-F2_TOM	0.194	0.230	0.643
RLIC-F3_ER	0.075	0.646	0.646
SCC-F1_MSCEIT	0.108	0.507	0.594
SCC-F2_TOM	0.100	0.539	0.594
SCC-F3_ER	0.087	0.594	0.594
SCR-F1_MSCEIT	0.102	0.529	0.793
SCR-F2_TOM	0.341	0.032	0.096
SCR-F3_ER	0.011	0.945	0.945
SFO-F1_MSCEIT	0.203	0.208	0.208
SFO-F2_TOM	0.280	0.080	0.134
SFO-F3_ER	0.272	0.089	0.134
SLF-F1_MSCEIT	0.041	0.801	0.801
SLF-F2_TOM	0.111	0.494	0.741
SLF-F3_ER	0.120	0.461	0.741
SS-F1_MSCEIT	0.182	0.261	0.783

SS-F2_TOM	0.103	0.527	0.790
SS-F3_ER	0.036	0.826	0.826
UNC-F1_MSCEIT	0.023	0.888	0.888
UNC-F2_TOM	0.350	0.028	0.083
UNC-F3_ER	0.042	0.795	0.888

Supplemental Table 9: Correlations between FW ROIs and social cognitive domains. Data was covaried for age, sex, and race. F1_MSCEIT= Emotion Management; F2_TOM= Theory of Mind; F3_ER= Emotion Perception. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

ROI-Social Cognition	r value	p-value	FDR p-value
ACR-F1_MSCEIT	-0.041	0.799	0.799
ACR-F2_TOM	-0.317	0.047	0.140
ACR-F3_ER	0.153	0.345	0.517
ALIC-F1_MSCEIT	-0.178	0.271	0.271
ALIC-F2_TOM	-0.305	0.056	0.169
ALIC-F3_ER	-0.223	0.166	0.248
AverageFW-F1_MSCEIT	-0.135	0.405	0.608
AverageFW-F2_TOM	-0.413	0.008	0.025*
AverageFW-F3_ER	-0.064	0.694	0.694
BCC-F1_MSCEIT	-0.111	0.496	0.505
BCC-F2_TOM	-0.224	0.164	0.492
BCC-F3_ER	0.108	0.505	0.505
CC-F1_MSCEIT	-0.037	0.819	0.819
CC-F2_TOM	-0.255	0.113	0.338
CC-F3_ER	0.078	0.633	0.819
CGC-F1_MSCEIT	-0.031	0.851	0.851
CGC-F2_TOM	-0.316	0.047	0.142
CGC-F3_ER	-0.044	0.785	0.851
CGH-F1_MSCEIT	-0.065	0.691	0.691
CGH-F2_TOM	-0.136	0.401	0.602
CGH-F3_ER	-0.333	0.036	0.109
CR-F1_MSCEIT	-0.185	0.252	0.378
CR-F2_TOM	-0.361	0.023	0.068
CR-F3_ER	0.037	0.819	0.819
CST-F1_MSCEIT	-0.205	0.205	0.307
CST-F2_TOM	-0.339	0.033	0.098

CST-F3_ER	-0.124	0.444	0.444
EC-F1_MSCEIT	-0.066	0.685	0.743
EC-F2_TOM	-0.279	0.081	0.243
EC-F3_ER	0.053	0.743	0.743
FX-F1_MSCEIT	0.012	0.942	0.942
FX-F2_TOM	-0.053	0.743	0.942
FX-F3_ER	0.060	0.712	0.942
FXST-F1_MSCEIT	-0.208	0.197	0.349
FXST-F2_TOM	-0.193	0.233	0.349
FXST-F3_ER	-0.116	0.476	0.476
GCC-F1_MSCEIT	-0.008	0.962	0.962
GCC-F2_TOM	-0.361	0.023	0.068
GCC-F3_ER	0.058	0.723	0.962
IC-F1_MSCEIT	0.017	0.915	0.915
IC-F2_TOM	-0.371	0.019	0.057
IC-F3_ER	-0.108	0.504	0.756
IFO-F1_MSCEIT	-0.062	0.703	0.703
IFO-F2_TOM	-0.205	0.203	0.460
IFO-F3_ER	-0.165	0.307	0.460
PCR-F1_MSCEIT	-0.147	0.363	0.545
PCR-F2_TOM	-0.414	0.008	0.025*
PCR-F3_ER	0.042	0.797	0.797
PLIC-F1_MSCEIT	0.118	0.467	0.562
PLIC-F2_TOM	-0.283	0.077	0.230
PLIC-F3_ER	0.094	0.562	0.562
PTR-F1_MSCEIT	0.037	0.820	0.820
PTR-F2_TOM	-0.271	0.091	0.272
PTR-F3_ER	-0.169	0.297	0.446
RLIC-F1_MSCEIT	0.106	0.512	0.687
RLIC-F2_TOM	-0.096	0.553	0.687
RLIC-F3_ER	-0.065	0.687	0.687
SCC-F1_MSCEIT	0.086	0.594	0.867
SCC-F2_TOM	-0.168	0.300	0.867
SCC-F3_ER	-0.027	0.867	0.867
SCR-F1_MSCEIT	-0.155	0.339	0.550
SCR-F2_TOM	0.010	0.951	0.951
SCR-F3_ER	-0.146	0.367	0.550
SFO-F1_MSCEIT	-0.244	0.129	0.386

SFO-F2_TOM	0.091	0.577	0.865
SFO-F3_ER	-0.025	0.877	0.877
SLF-F1_MSCEIT	-0.085	0.601	0.706
SLF-F2_TOM	0.185	0.252	0.706
SLF-F3_ER	-0.061	0.706	0.706
SS-F1_MSCEIT	0.009	0.954	0.954
SS-F2_TOM	-0.186	0.251	0.752
SS-F3_ER	0.031	0.849	0.954
UNC-F1_MSCEIT	-0.065	0.691	0.691
UNC-F2_TOM	-0.143	0.377	0.691
UNC-F3_ER	-0.077	0.638	0.691

Supplemental Table 10: Correlations between FAt ROIs and clinical measures. Data was covaried for age, and sex. SAPS= Scale for the Assessment of Positive Symptoms; SANS= Scale for the Assessment of Negative Symptoms. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

ROI-Clinical Symptoms	r value	p-value	FDR p-value
ACR-SAPS	0.260	0.084	0.169
ACR-SANS	-0.092	0.545	0.545
ALIC-SAPS	-0.001	0.997	0.997
ALIC-SANS	-0.072	0.636	0.997
AverageFAt-SAPS	0.159	0.297	0.297
AverageFAt-SANS	-0.176	0.247	0.297
BCC-SAPS	0.299	0.046	0.092
BCC-SANS	-0.072	0.639	0.639
CC-SAPS	0.272	0.071	0.141
CC-SANS	-0.139	0.360	0.360
CGC-SAPS	0.257	0.089	0.177
CGC-SANS	-0.059	0.698	0.698
CGH-SAPS	-0.219	0.147	0.294
CGH-SANS	-0.109	0.476	0.476
CR-SAPS	0.193	0.204	0.408
CR-SANS	-0.119	0.433	0.433
CST-SAPS	-0.124	0.416	0.833
CST-SANS	-0.002	0.989	0.989
EC-SAPS	-0.027	0.859	0.859
EC-SANS	-0.181	0.233	0.466

FX-SAPS	0.215	0.156	0.312
FX-SANS	-0.020	0.897	0.897
FXST-SAPS	-0.041	0.788	0.788
FXST-SANS	-0.082	0.591	0.788
GCC-SAPS	0.231	0.127	0.254
GCC-SANS	-0.005	0.972	0.972
IC-SAPS	0.034	0.824	0.824
IC-SANS	-0.138	0.366	0.733
IFO-SAPS	0.093	0.542	0.542
IFO-SANS	-0.123	0.420	0.542
PCR-SAPS	0.213	0.160	0.298
PCR-SANS	-0.158	0.298	0.298
PLIC-SAPS	-0.033	0.832	0.832
PLIC-SANS	-0.108	0.478	0.832
PTR-SAPS	0.186	0.220	0.441
PTR-SANS	-0.067	0.661	0.661
RLIC-SAPS	0.113	0.457	0.457
RLIC-SANS	-0.225	0.137	0.273
SCC-SAPS	0.069	0.653	0.653
SCC-SANS	-0.249	0.099	0.198
SCR-SAPS	0.110	0.472	0.616
SCR-SANS	-0.077	0.616	0.616
SFO-SAPS	0.085	0.577	0.848
SFO-SANS	-0.029	0.848	0.848
SLF-SAPS	0.318	0.034	0.068
SLF-SANS	-0.038	0.805	0.805
SS-SAPS	0.057	0.708	0.708
SS-SANS	-0.200	0.188	0.376
UNC-SAPS	-0.123	0.419	0.419
UNC-SANS	-0.133	0.381	0.419

Supplemental Table 11: Correlations between FW ROIs and clinical measures. Data was covaried for age, and sex. SAPS= Scale for the Assessment of Positive Symptoms; SANS= Scale for the Assessment of Negative Symptoms. * indicates $p < 0.05$ for FDR correction for multiple comparisons.

ROI-Clinical Symptoms	r value	p-value	FDR p-value
ACR-SAPS	-0.160	0.292	0.585
ACR-SANS	-0.015	0.923	0.923
ALIC-SAPS	0.241	0.110	0.221
ALIC-SANS	0.140	0.358	0.358
AverageFW-SAPS	-0.222	0.143	0.286
AverageFW-SANS	0.012	0.936	0.936
BCC-SAPS	-0.082	0.593	0.593
BCC-SANS	-0.170	0.264	0.528
CC-SAPS	-0.103	0.498	0.498
CC-SANS	-0.135	0.374	0.498
CGC-SAPS	-0.146	0.337	0.674
CGC-SANS	-0.001	0.994	0.994
CGH-SAPS	-0.026	0.864	0.864
CGH-SANS	0.063	0.682	0.864
CR-SAPS	-0.148	0.329	0.658
CR-SANS	-0.050	0.745	0.745
CST-SAPS	0.232	0.124	0.142
CST-SANS	0.222	0.142	0.142
EC-SAPS	-0.011	0.942	0.942
EC-SANS	0.337	0.024	0.048*
FX-SAPS	-0.132	0.387	0.774
FX-SANS	-0.039	0.799	0.799
FXST-SAPS	0.031	0.841	0.995
FXST-SANS	0.001	0.995	0.995
GCC-SAPS	-0.044	0.772	0.772
GCC-SANS	-0.074	0.627	0.772
IC-SAPS	0.015	0.923	0.923
IC-SANS	0.027	0.861	0.923
IFO-SAPS	-0.176	0.247	0.494
IFO-SANS	0.065	0.671	0.671
PCR-SAPS	-0.054	0.725	0.725
PCR-SANS	-0.089	0.558	0.725

PLIC-SAPS	0.083	0.586	0.859
PLIC-SANS	0.027	0.859	0.859
PTR-SAPS	0.036	0.812	0.812
PTR-SANS	-0.087	0.571	0.812
RLIC-SAPS	-0.065	0.671	0.671
RLIC-SANS	-0.115	0.449	0.671
SCC-SAPS	-0.098	0.522	0.948
SCC-SANS	0.010	0.948	0.948
SCR-SAPS	0.118	0.440	0.880
SCR-SANS	0.008	0.961	0.961
SFO-SAPS	-0.116	0.447	0.447
SFO-SANS	-0.272	0.071	0.143
SLF-SAPS	-0.049	0.750	0.950
SLF-SANS	-0.010	0.950	0.950
SS-SAPS	-0.276	0.067	0.134
SS-SANS	-0.024	0.876	0.876
UNC-SAPS	-0.159	0.297	0.593
UNC-SANS	0.012	0.936	0.936

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