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Neural Underpinnings of Social Withdrawal Analyzed Through Schizotypy

Jesse Edmond

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by

Jesse Edmond

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ABSTRACT

Schizotypy is a set of personality traits that may predispose someone to develop a schizophrenia spectrum disorder. Social withdrawal is common in schizotypy and typically results in a lack of close relationships, little social support, and can exacerbate pre-existing psychiatric symptoms. White matter plays an integral role in cognition, yet it is still not understood which tracts influence social withdrawal. By collaborating with the ENIGMA Schizotypy working group, we gathered social withdrawal scores from the Community Assessment of Psychic Experiences and diffusion tensor imaging data from 375 participants. Using the ENIGMA DTI Pipeline, we were able to measure fractional anisotropy in six tracts and regress these numbers against social withdrawal scores. We studied the superior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, cingulum bundle, and the splenium of the corpus callosum. Through this analysis, we analyzed the relationship of white matter integrity and social withdrawal through the lens of schizotypy.

INDEX WORDS: Diffusion tensor imaging, Social withdrawal, Schizotypy, White matter, Community assessment of psychic experience, Enhancing neuro imaging genetics through meta analysis

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by

Jesse Edmond

Committee Chair: Jessica Turner

Committee: Gemma Modinos

Tricia King

Electronic Version Approved:

Office of Graduate Services

College of Arts and Sciences

Georgia State University

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DEDICATION

I would like to dedicate this thesis to my parents, John and Lisa Edmond, who always encouraged me to challenge myself and never give up.

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1 INTRODUCTION

1.1 Dimensional Model of Schizotypy

The continuum model of schizotypy posits that, within a population, there exists a set of traits analogous to those of schizophrenia which, at an extreme level, may predispose someone to developing a serious disorder that lies on the schizophrenia spectrum (Debbane, 2015; Holt, 2020; Lenzenweger, 2006; Lenzenweger, 2018; Meehl, 1962; Nelson et al., 2013).These traits include odd or bizarre behavior, strange speech, magical thinking, unusual perceptual experiences, and social anhedonia (Nelson et al., 2013). Although they may be liable to develop a disorder, those with schizotypy do not necessarily have an illness and only a subset may later develop one (Lenzenweger, 2006; Meehl, 1962).

Schizotypy is considered to consist of three trait dimensions similar to those of schizophrenia, as reviewed by Debbane et al., (2015) and Nelson et al., (2013). First is the cognitive-perceptual dimension which corresponds to the positive symptoms of schizophrenia. This dimension includes magical thinking, unusual perceptual experiences, ideas of reference, and paranoia. The interpersonal dimension corresponds to the negative symptoms of schizophrenia and includes constricted affect, social anxiety, lack of close personal relationships, and suspiciousness. Lastly, the disorganized dimension includes odd behavior and speech traits.

How these traits are distributed throughout the general population is still debated. Based on Meehl's original quasi-dimensional theory, approximately 10% of the population possesses this organization of personality traits that puts them at risk of developing psychosis (Holt, 2020; Nelson et al., 2013). Although this is the oldest model of schizotypy, studies focusing on this aspect have recently gained criticism due to poor sampling methods and procedures (Nelson et al., 2013). A newer model of schizotypy, the fully dimensional approach, insists that schizotypy

is a trait that can be found throughout the population and is not inherently dangerous (Holt, 2020; Nelson et al., 2013). In this model, schizotypy is thought of as a continuum. Those on the low end of this continuum can be perfectly healthy, functioning individuals, while those on the high end may possibly develop debilitating psychosis and even a schizophrenia spectrum disorder. This view falls in line with current schizophrenia theories in that there is a continuity among clinical and non-clinical populations as well as the three-factor structure of schizophrenia and psychosis (Nelson et al., 2013). For the purposes of this study, we will be using the fully dimensional view of schizotypy, insisting that the population falls within a continuum, and those at the extreme high end are at risk of developing a severe psychological disorder.

1.2 Social Withdrawal in Schizotypy

Those on the extreme high end of this continuum may develop psychosis or any disorder on the schizophrenia spectrum such as schizotypal personality disorder or schizoaffective disorder (Nelson et al., 2013). Research analyzing which aspects of schizotypy may best represent who will "convert" to a more serious illness has been conducted. Kwapil et al. (2013) found that traits from both the cognitive-perceptual and interpersonal dimensions predicted the development of schizophrenia-spectrum disorders to a greater extent than family history when analyzing data from a ten-year longitudinal study. Debbane et al. (2015) found similar results in a general population study. It was also found that those with higher interpersonal dimension traits were more likely to lack close relationships (Kwapil et al., 2013). This is an important indication, as those with more significant interpersonal deficits tend to become socially withdrawn, which can cause further problems in already existing conditions (Porcelli et al., 2019).

Those with schizotypy, as well as schizophrenia spectrum disorders, are known to be socially isolated and suffer from social dysfunction and, despite a desire to do so, may fail to relate to and create close bonds with others (Gabbard et al., 2012; Kwapil, 1998). This is problematic as humans are innately social creatures, so much so that it has been speculated that social dilemmas and the need to solve them may have played an integral role in the evolution of the human brain (Porcelli et al., 2019). A lack of social support can be detrimental to one's mental health regardless of whether they have a pre-existing condition and utilizing schizotypy allows us to study subclinical manifestations of these traits as well as the prodrome, spectrum disorders, and psychosis (Holt, 2020; Kwapil et al., 2013; Porcelli et al., 2019). From this perspective, it is easy to understand why it is critical to decipher how social withdrawal (SW) can manifest. There is an argument for understanding why some people seem willing and able to reach out to others and build meaningful relationships while others are completely reluctant to do so even though it can be detrimental to their wellbeing.

The social brain is comprised of different networks that work together to help individuals relate to and understand those around them. The mirroring network is largely responsible for answering why someone is performing an action or understanding someone's basic emotions (Porcelli et al., 2019; Rizzolatti & Sinigalia, 2016; Wang et al., 2018). The mentalizing network, on the other hand, helps to understand the causes and consequences of someone's actions or emotions as well as predicting the behaviors of others (Porcelli et al., 2019; Wang et al., 2018). The perception network allows one to detect important stimuli such as facial expressions and body language (Porcelli et al., 2019; Wang et al., 2018). All of these networks are important in facilitating healthy social interaction, however, dysfunction within these networks can lead to

problems. Before we further explain the neural mechanisms of these social networks, we will first discuss the method of measurement used in this study, diffusion tensor imaging (DTI).

1.3 Diffusion Tensor Imaging and Its Use in Analyzing White Matter

DTI is a technique that allows one to analyze the diffusion of water in the brain's white matter (O'Donnell & Westin, 2011; Soares et al., 2013). Typically, water molecules diffuse freely in all directions, known as isotropic diffusion, however, this is not the case for all brain tissue. Due to cellular structure, myelination, and the packing of axons, water within the brain's white matter diffuses along the axon in what is known as anisotropic diffusion (O'Donnell & Westin, 2011; Soares et al., 2013). Water in gray matter will diffuse less anisotropically and water in cerebrospinal fluid is completely unrestricted and therefore diffuses isotropically. Measuring the diffusivity of water within white matter, DTI offers a way for us to study its architecture (O'Donnell & Westin, 2011). It also allows us to indirectly analyze alterations to the architecture that may arise due to conditions or physical damage as well as analyze myelination levels (Soares et al., 2013).

In a similar fashion to magnetic resonance imaging, DTI uses magnetic field gradients to examine the diffusion of water in a certain direction and then produce a three-dimensional, ellipsoid model of this diffusion known as a tensor (O'Donnell & Westin, 2011; Soares et al., 2013). Because DTI is essentially a different form of magnetic resonance imaging, it requires no new equipment, contrast agents, or chemical tracers (Soares et al., 2013). The entire process is performed by introducing different gradient pulses that cancel out water molecules that are not diffusing while causing a phase shift in the molecules that do diffuse (O'Donnell & Westin, 2011). Between the application of two pulses, water protons that maintain their position will experience no diffusion-related dephasing while protons that do diffuse away from their starting

point will experience an incomplete reversal of diffusion-related dephasing (Yang et al., 2011). This reversal causes a proportionate loss of signal creating darker voxels in the white matter tracts (O'Donnel & Westin, 2011; Yang et al., 2011).

The most common model of measuring diffusion describes water diffusion using three orthogonal gaussian distributions with coefficient magnitudes of λ_1, λ_2, λ_3 (Yang et al., 2011). Using these magnitudes, the shape of diffusion can be determined. For instance, if all three coefficients are equal, the diffusion is spherical, or isotropic. Based on the differences between these values, the shape of diffusion will become more ellipsoidal. It is these three magnitudes that make up three separate vectors used to produce the diffusion tensor mentioned above (Yang et al., 2011). The DTI process results in different, useful measures of diffusion. First is mean diffusivity (MD), which is simply the average of the three coefficients and describes the total amount of diffusion in a voxel and is related to the amount of water in extracellular space (O'Donnel &Westin, 2011). Next, fractional anisotropy (FA) is the difference of the tensor's ellipsoid from a perfect sphere and is the most widely used measure of anisotropy (O'Donnell & Westin, 2011). A FA value of zero signifies a perfectly spherical tensor i.e., isotropic diffusion, and a value close to one means that diffusion in the principal direction (λ_1) is much greater than the other two directions i.e., anisotropic diffusion (Yang et al., 2011). Average, healthy, white matter should have higher FA values and low MD as they are essentially opposite measures of each other. Finally, axial, and radial diffusivity can also be measured. Axial diffusivity (AD), which is equal to the largest coefficient, is diffusion that is parallel to the white matter tract and radial diffusivity (RD), which is equal to the average of the two smaller coefficients, is diffusion that is perpendicular to the tract (O'Donnell & Westin, 2011). Using all four of these measures

we can evaluate the architecture of different white matter tracts of the brain and determine their integrity.

1.4 The Effects of Poor White Matter Integrity

The integrity of white matter tracts is an important characteristic that has been linked to deficits in cognition, mood alterations, behavior, and symptoms in a number of different disorders (Filley & Fields, 2016; Haznedar et al., 2005; Kelly et al., 2018; Nakamura et al., 2012; Waller et al., 2017). White matter refers to the neurons that connect different regions of the brain and aid in the sending of signals between these different regions. It consists of an axon wrapped in a white, fatty substance known as myelin. This substance has an important role in facilitating proper signal transmission and communication within these axons and therefore is integral in daily functioning and cognition (Filley & Fields, 2016; Roalf et al., 2015).

The frontal lobes of the brain are the last section to be fully myelinated, which does not occur until roughly 25 years of age and possibly into the 30's (Fields, 2008; Larsen & Luna, 2018; Sampaio-Baptista & Johansen-Berg, 2017). Due to the role white matter plays in communication and how myelination occurs, researchers believe that it may be the cause of adolescents' lack of proper reasoning and behavior relative to fully grown adults (Giedd, 2004; Oyefiade et al., 2018). When compared directly to adults, adolescents were shown to have less restricted diffusion, which was associated with slower reaction times and decision making (Liston et al., 2006; Oyefiade et al., 2018). These findings support the idea that white matter has a significant impact on day-to-day life and therefore it is easy to understand how disruptions in this area could lead to problems in daily functioning and cognition.

When white matter begins to degrade, different problems can arise. Poor white matter integrity can ultimately damage neurocognitive performance and other mental functions (Roalf et

al., 2015). Many disorders are linked to poor integrity of white matter tracts such as Alzheimer's disorder, schizophrenia, bipolar spectrum illnesses, autism spectrum disorder, and antisocial behavior (Filley & Fields, 2016, Kelly et al., 2018; Koshiyama et al., 2020; Nakamura et al., 2012; Waller et al., 2017). These studies use water diffusion as the main method of measuring white matter integrity with FA being the most common measure, but measures of AD and RD were also used. Researchers found significant differences in one or more of these measures between healthy controls and the psychiatric population of interest.

The impact of white matter in everyday life and psychiatric disorders should not be understated. This area of research has had numerous findings to support its importance yet there is still work to be done in further elucidating white matter abnormalities responsible for these different disorders. Schizotypy is one such area that still needs proper identification of these diffusivity abnormalities.

1.5 White Matter Tracts Implicated in Schizotypal Symptom Severity

As mentioned above, schizotypy consists of three trait dimensions that are similar to the positive, negative, and disorganized symptom dimensions of schizophrenia (Debbane et al., 2015; Nelson et al, 2013). Despite the similarities of schizotypy and schizophrenia, there have not been many DTI studies analyzing white matter of schizotypy (DeRosse et al., 2015; Lener et al., 2015; Liu et al., 2016; Nelson et al., 2011). Given that schizotypy may predispose an individual to develop schizophrenia, understanding its physical underpinnings is a logical step towards better understanding spectrum disorders and psychosis.

Overlapping white matter tracts that are implicated in schizotypy and schizophrenia have been studied, but these studies are few and far between (DeRosse et al., 2015; Lemaitre et al., 2018; Pfarr & Nenadić, 2020). DeRosse et al. (2015) found that, those who were considered to

have more severe schizotypy had a decrease in inferior fronto-occipital fasciculus (IFOF) FA compared to those with low schizotypy. This group also found the left uncinate fasciculus (UF) to be implicated in high schizotypy. Nelson et al., (2011) found associations between the integrity of the UF, right superior longitudinal fasciculus (SLF), and left cingulum (CB), and cognitive-perceptual schizotypy. Lemaitre et al. (2018) also found an association between alterations in the left UF and cognitive-perceptual schizotypy. Significant correlations between lower FA in the right superior longitudinal fasciculus (SLF) and disorganized schizotypy have been found; as have significant correlations between interpersonal schizotypy and the SLF, right anterior thalamic radiation (ATR), right IFOF, and right UF (Pfarr & Nenadić, 2020)

It is plain to see there is an agreement in the research that the IFOF and UF have a significant role in schizotypy, yet what aspect of schizotypy they influence has not been completely deciphered. This case is most evident in the UF with two of the groups stating that the UF plays a role in cognitive-perceptual and interpersonal schizotypy. Despite this inconsistency, these results do overlap with those of the largest schizophrenia meta-analysis to date (Kelly et al., 2018). These findings further support the relation between schizotypy and schizophrenia in that underlying neurobiological bases seem to be rather similar.

As previously stated, the work in this area is relatively sparse and there is still a need to understand the development of schizophrenia spectrum disorders. Studying a subclinical population allows researchers to examine psychotic-like symptoms without having to parcel out effects of medication, institutionalization, and co-morbidities (Barrantes-Vidal et al., 2015; Kwapil et al., 2013; Lemaitre et al., 2018; Nelson et al., 2011). Research in this area would be advantageous, but the proposed study intends to delve deeper than simply studying which white matter tracts are implicated in schizotypy. The social deficits of schizophrenia spectrum

disorders, as mentioned above, have compounding effects on an individual's mental health. For this reason, we are interested in which tracts influence the social deficit traits seen in those with schizotypy.

1.6 White Matter in Social Withdrawal and Connections to Schizotypy

The current understanding of how white matter affects SW and social cognition, in general, is limited (Wang et al., 2018; Wang & Olson, 2018). As of 2018, there have been four times as many studies detailing the role of gray matter in the area as there have been studies focusing on white matter (Wang & Olson, 2018). The study of white matter in social cognition is imperative. The number of processes the brain must perform to effectively interact in a social environment requires efficient communication across the entire brain (Wang & Olson, 2018).

1.6.1 Facial Perception Network

When discussing social cognition, it is important to understand the "social brain." This begins with the facial perception network. This is where most interactions begin; perceiving another's face and other information such as eye movement or facial expressions (Porcelli et al., 2019; Wang et al., 2018). Two tracts make up the main bundles of this network, the inferior longitudinal fasciculus (ILF) and the IFOF (Wang et al., 2018). The ILF and IFOF connect temporal and occipital regions that are involved with visual recognition (Latini, 2015; Waller et al., 2017). The integrity of both the ILF and IFOF have been implicated in the ability to properly identify affect displayed by facial expressions, poor social interaction scores in those with autism, and antisocial behavior (Im et al., 2018; Rigon et al., 2019; Waller et al., 2017). A third tract, the SLF, which connects frontal, temporal, and parietal lobes, has also been linked to facial processing in social cognition as well as poor social interaction in autism and general antisocial

behavior (Im et al., 2018; Waller et al., 2017; Wang et al., 2018). The role of the SLF in social cognition expands even further into the mirroring network.

1.6.2 The Mirroring Network

The mirroring network allows us to use the movements of others i.e., body language, to simulate and interpret the actions and emotions of others (Porcelli et al., 2019). Observing and paying attention to someone's body language and displays of emotion gives a glimpse into that person's affective states and can activate similar networks or brain regions as the person performing these actions (Rizzolatti & Sinigaglia, 2016). The SLF is the main tract that supports this network, however, the UF, ATR, and fornix are all involved with interpreting another person's actions (Wang et al., 2018). The UF connects the frontal and temporal lobes and, along with being involved in antisocial behavior and poor social interaction in autism, has been implicated in social cognition in that better integrity of this tract was linked to better social cognition in healthy and experimental groups (Im et al., 2018; Jalbrzikowski et al., 2014; Olszewski et al., 2017; Waller et al., 2017). Abnormal integrity of the ATR, which has also been linked to social deficits in autism and general antisocial behavior, was shown to be related to deficits in emotion identification as measured by the Awareness of Social Inference Test (TASIT) (Downey et al., 2015). Lastly, the fornix, a core part of the limbic tract, has also been implicated in emotion identification in that lower FA was associated with poorer scores on the TASIT (Downey et al., 2015; McDonald et al., 2019).

1.6.3 The Mentalizing Network

The mentalizing network allows an individual to infer the reasons behind someone's behaviors, actions, and emotional states as well as the consequences while also allowing for the prediction of future behaviors (Porcelli et al., 2019; Wang et al., 2018). Damage in the arcuate

fasciculus (AF) has been shown to be associated with poorer mentalizing abilities as has damage in the SLF (Herbet et al., 2014). The CB, SLF, AF are the most important tracts in this network. The CB, another region of the limbic system, connects the medial prefrontal cortex and the medial posterior parietal cortex (Herbet et al., 2014). In a study examining the integrity of white matter and social network size, a marker of social abilities, researchers found that higher measures of FA within the CB were linked to having larger social networks (Noonan et al., 2018).

The CB is located close to the corpus collosum, and sections of the cingulum intersect with different regions of this tract, including the splenium (SCC) (Knyazeva, 2013; Wu et al., 2016). Given the importance of the CB in social cognition and evidence that the corpus callosum is implicated in these processes and associated with social network size, it may be that both regions have an important role in social deficits seen in schizotypy (Noonan et al., 2018; Waller et al., 2017). Though the SCC was not brought up in previous schizotypy research, it should be noted that Kelly et al. (2018) did find negatively trending associations between this tract's integrity and the negative symptoms of schizophrenia.

Many of the white matter tracts involved in social cognition have been implicated in schizotypy. The IFOF, UF, and SLF have all been found to be altered in those on the high end of the continuum. Due to these tracts' importance in the different aspects of social cognition, it is not unreasonable to think that the abnormalities found in these pathways may be linked to the social deficits that are prevalent in those who are on the extreme ends of the schizotypy continuum. The above paragraphs have pointed to a number of different studies that show how social cognition relies on the health of these tracts. Further, given the importance of the CB in social cognition and its close proximity to the SCC, these two tracts may very well have a large

role in the social deficits of this population. The proposed study attempts to determine if there is a relationship between these tracts and the SW traits seen in a subclinical schizotypy population by analyzing FA and MD measures.

Aim 1: Disentangle contributions to social withdrawal of other white matter tracts, mainly the SLF, IFOF, UF as well as the CB.

Hypothesis 1a: Lower FA in these tracts will be associated with more severe SW scores as measured by the Community Assessment of Psychotic Experiences (CAPE).

Hypothesis 1b: Higher MD in these tracts will be associated with more severe SW scores as measured by the CAPE.

Aim 2: Determine the role of white matter integrity of the SCC in individual personality traits of social withdrawal.

Hypothesis 2a: Lower FA in the splenium of the corpus callosum will be associated with higher levels of SW as measured by CAPE.

Hypothesis 2b: Higher MD in the splenium will be associated with higher levels of SW as measured by the CAPE.

2 METHODS

2.1 Participants

Participant data were acquired through the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) Schizotypy working group using their legacy datasets. The sample consisted of 375 nonclinical participants with DTI data and CAPE measurements from Melbourne, Australia. Sabaroedin et al., (2019) recruited 672 participants from the general population, of this sample, 414 underwent diffusion protocols and CAPE testing. Inclusion criteria of this study involved participants being right-handed, 18-50 years of age, and all four grandparents being of European descent. Exclusion criteria consisted of having a history of neurological or psychiatric illness, regular use of recreational drugs for at least one month or a history of drug abuse, and a significant blow to the head resulting in loss of consciousness or memory. Participants were assessed on these criteria based on a screening questionnaire and self-report responses. Of these 414 participants, 39 were excluded due to artifacts including, low signal-to-noise, slice dropouts, and or excessive movement. The final 375 participants included 160 males with a mean age of 22 years. The study was conducted in accordance with the Monash University Human Research Ethics Committee and each participant provided written informed consent. See Table 1 for a complete list of demographics and variables.

Table 1 Demographics

Variable	Range	Average
Gender	160 Male / 215 Female	
Age	18 – 50	23.38
Social Withdrawal	2.5 – 9.58	4.321
CAPE Total	43 – 107	63.28
Average FA	.3907 - .4678	.4268

SLF FA	.4358 - .5478	.4867
IFOF FA	.3895 - .6135	.4867
UF FA	.3477 - .6019	.4625
CB FA	.4624 - .6338	.5506
SCC FA	.6456 - .7607	.7204
Average MD	.00052 - .0006	.0006
SLF MD	.00046 - .00054	.0005
IFOF MD	.00054 - .00066	.0006
UF MD	.00052 - .0007	.0006
CB MD	.00049 - .00057	.00052
SCC MD	.00046 - .00058	.0005

2.1.1 Sensitivity Analysis

To identify the effect size of the study, a sensitivity analysis was performed using G*Power (Faul et al., 2009). Given that there are six tracts of interest, an α level of .05 was divided by 6 resulting in an α level of .0081, and a power of .80 was chosen. Using these parameters, the detectable effect size for the Melbourne sample was .035 (Cohen's f^2 = .035 for a sample size of 353). The previous studies analyzing white matter and schizotypy discussed above included samples ranging from 97 to 138, two of which performed regressions of white matter integrity and general schizotypy dimensions; neither of these studies discussed their effect sizes (DeRosse et al., 2015; Lemaitre et al., 2018; Pfarr & Nenadić, 2020). Given that the effect sizes of Cohen's f^2 range from small of .02, medium of .15, and large of .30, we clearly had an effect size within the small to medium range (Aguinis et al., 2005; Selya et al., 2012). These small effect sizes coupled with a power of .80 indicate that our study was adequately powered to find an effect even if it is relatively small.

2.2 Diffusion Tensor Imaging Acquisition

Images were acquired at Monash Biomedical Imaging in Clayton, Victoria Australia on a Siemens Skyra 3T scanner with a 32-channel head coil (Oldham et al., 2020). Images were acquired in an interleaved fashion. Diffusion data was acquired using 60 gradient directions with b = 3000 s/mm^2 and 7 with b = 0 s/mm^2. The parameters included a TR = 8800 ms, TE = 110 ms, and FOV = 240 mm.

2.3 Community Assessment of Psychic Experience and Social Withdrawal Factor Scores

The Assessment of Psychotic Experiences (CAPE) was used to measure levels of schizotypy within their participants. Stefanis et al. (2002) were concerned about the lack of depression measures in schizotypy scales despite the symptom being associated with schizotypy. This led them to include measures of depression with other dimensions to create what would become the CAPE. Furthermore, they intended for this new scale to measure the psychotic symptoms to better understand what symptoms clinical patients might be experiencing. The goal of this second approach was to make it easier to compare patients with the general population. This group believed that, within the general population, there were three dimensions of psychosis: positive, negative, and depressive. A confirmatory factor analysis was used to compare this three-dimensional model to two- and single-dimension models.

The basis of this scale was the Peters Delusional Inventory-21; however, some modifications were introduced. First, any items regarding religious delusions were removed. Second, any items that were previously reported as being ambiguous were removed or rephased. Third, two items on auditory hallucinations were added. And lastly, the items on this scale had two-dimensional scales each. The first scale regarded the frequency of an experience on a scale of “never,” “sometimes,” “often,” and “nearly always.” The second scale detailed the level of

distress an experience created on a scale of "not distressed," "a bit distressed," "quite distressed," and "very distressed."

In addition to a confirmatory analysis, Stefanis et al., (2002) also performed validity analyses on the individual dimensions of the CAPE. To assess the depression dimension, they used the Depression scale of the Symptom Checklist-90; for the positive scale they used the Perceptual Aberration Scale and the Symptom Checklist-90 Paranoia subscale; and to validate the negative dimension the Social Isolation and Flat Affect subscales of the Schizotypal Personality Questionnaire was used. A multivariate regression analysis was carried out for each dimension. The CAPE's clinical validity was analyzed by testing for associations between the frequency and distress scales of each item.

Results of these analyses found that, in terms of frequency, the three-factor model provided the best fit to the data compared to the two- or single-dimension models. The individual dimensions were found to co-vary with each other with variation in one dimension explaining around 50% of the variance in another. The positive, negative, and depressive dimensions of the CAPE were found to be strongly associated with their respective established scales, establishing their validity. A correlation of 0.71 was found between the frequency and distress scales.

The initial study of the CAPE found that the three dimensions of the new scale fit the data and had both discriminant and clinical validity. In 2016, Mark and Toulopoulou re-tested the reliability and validity of the CAPE to reaffirm its psychometric properties in a meta-analysis. Mark and Toulopoulou analyzed 111 studies published between 2002 and 2014 that used the CAPE and found that scores were reliable and that the scale was reliable across age groups. All previous exploratory and confirmatory factor analyses found a three-dimensional structure similar to the original structure of Stefanis et al. (2002). In studies that included

reliability coefficients, it was found that most had Cronbach's alpha levels above .7, leading the authors to state that the CAPE can provide reliable scores on positive and negative psychotic-like experiences.

The use of the CAPE is advantageous as it also allows for the measure of SW within individuals (Ziermans, 2013). In this study, Ziermans originally intended to study the relationship between working memory and psychotic-like experiences. 1087 participants were assessed using the CAPE and factor analyses were performed on the individual subscales. This analysis resulted in a three-factor model of the negative symptom scales, one of which was a SW factor. This factor consists of questions 3, 4, 16, and 29 of the CAPE. This factor structure was later confirmed by Mark and Toulopoulou (2016) using eigenvalues, scree test, and Monte Carlo simulations. It is this SW factor that will be used to measure the SW levels within our sample and regressed against DTI measures found using the ENIGMA pipeline.

2.4 ENIGMA Diffusion Tensor Imaging Pipeline

This study used the ENIGMA DTI Pipeline to calculate FA and MD values. Jahanshad et al. (2013) set out to create a unified protocol to reduce discrepancies between sets of data imaged with different protocols. The group used 100 different FA images from four separate cohorts to create a new target image in MNI space using previously established white matter atlases. The newly formed FA template was registered to the John Hopkins University (JHU) DTI atlas to form a custom mean atlas. The new template was also skeletonized to reveal the core of the white matter. This skeleton can be used for tract-based spatial statistics. Further, the new target image was parcellated into regions of interest (ROI) based on the JHU atlas as well. Overall, it was shown that data sets registered to the ENIGMA DTI template showed registration

improvements compared to those registered to the existing JHU template. This process has been successfully used to study the heritability of FA and the connection between FA and schizophrenia symptom severity (Kelly et al., 2018; Kochunov et al., 2015).

2.4.1 Pre-Processing

DTI data acquired by the different sites must first be converted from raw Digital Imaging and Communications in Medicine (DICOM) image file to FA images. This step, along with quality control, is referred to as pre-processing. The conversion can be completed using a command such as dicom2niigui from the Neuroimaging Tools and Resources Collaboratory. This will convert all DTI images into a Neuroimaging Informatics Technology Initiative (NIfTI) file needed for the analysis. During this stage, the number of b-values must be calculated. These values include the b=0 which is a reference image that has not had a diffusion gradient applied and the b-value that represents the strength of the gradient that has been applied during the acquisition (O'Donnell & Westin, 2011). Once this has been completed a quality check must be performed to ensure that the applied gradients align to the FA image.

After converting DICOM to FA images and checking the gradients, an eddy correction must be performed. When the diffusion encoding gradients change during the acquisition process, an eddy current is induced creating a magnetic field (Andersson & Sotiropoulos, 2016). This magnetic field can create artifacts within the DTI image that need to be corrected. The ENGIMA DTI pipeline does not call for any specific eddy correction but recommends using the FMRIB Software Library's (FSL) eddy_correct command (Andersson & Sotiropoulos, 2016; Smith et al., 2004). This tool models the effects of eddy currents as well as movement and then replaces any affected slices with non-parametric predictions using the Gaussian Process.

The next pre-processing step is brain extraction. This step is essentially removing any non-brain tissue, such as the skull and eyeballs, from the image and results in a brain mask. One possible method is using FSL's Brain Extraction Tool (BET) (Smith, 2002). BET first estimates a set of parameters that will be used throughout the process. These include robust image intensity minimum and maximum, a threshold to distinguish between brain matter and background, the center of gravity of the brain, and the mean radius of the brain. Next, the brain surface must be modeled. This is done using connected triangles to perform a surface tessellation. This process is centered around the center of gravity with the radius being half that of the brain radius. Each triangle is subdivided into smaller triangles until a spherical surface is formed. To find the best position, each vertex of the triangles must be moved, this process is performed up to 1,000 times. Once this update is complete, BET will force the model to fit the real brain surface. Once the surface model is complete, BET checks to ensure that there are no portions that self-intersect. This tool only leads to self-intersection about 5% of the time but if there are self-intersections, BET can be re-run with higher smoothness constraints. BET has been checked against two other methods, Analysis of Functional Neuro Images and Brain Surface Extractor, and was found to lead to the lowest number of errors using both automated and hand-optimized methods. Altogether, BET has been tested on thousands of datasets, takes only a few seconds to run, and has been shown to be robust and accurate. Once completed, the resulting images can be checked using FSL to ensure that any non-brain material was removed while not removing any brain material.

The last step in pre-processing is fitting each voxel to a diffusion tensor model. To do this, we use the FSL Diffusion Toolbox (FDT) and the DTIFIT tool within it. This step requires the ".bvec" and ".bval" files created in the conversion step, an "_ecc" file created during eddy

correction, and a “brain_mask” file created during the BET step. This last step results in the eigenvectors and eigenvalues used to create the FA maps and tensors. Once completed, the resulting diffusion tensors can be viewed in FSL. If the pre-processing was run correctly, the image should include a map of white matter tracts with green, red, and blue lines indicating which tracts run anterior to posterior, left to right, and dorsal to ventral respectively. Following the pre-processing, the FA images must be skeletonized.

2.4.2 ENIGMA Diffusion Tensor Imaging Skeletonization

The skeletonization process allows for all FA images to be registered and skeletonized to the ENIGMA DTI atlas. First, all FA images are grouped together in a single folder and then slightly eroded to remove likely outliers from the diffusion tensor fitting. Next, nonlinear registration is performed to align FA images to a standard space followed by nonlinear transformations. The mean of all FA images is calculated to create a “mean_FA” image which will be used to create the skeleton. A quality check must be performed to ensure proper registration; if there was poor registration, the ENIGMA DTI templates must be re-masked. Using the mean_FA image, a skeleton will be created which will itself be used to create a distance map. This distance map will be used to project FA images onto the skeleton. These projection values are what will be used in statistical analyses.

2.4.3 ENIGMA Diffusion Tensor Imaging Region of Interest Extraction

The last step in the pipeline extracts relevant ROIs from the skeletonized FA images. A spreadsheet containing relevant covariate data, such as age and sex, is created prior to this step. This process is performed in R Studio and begins with extracting all ROI values from the JHU atlas and average FA values across the skeleton. The output is a csv file with the mean FA values of the ROIs for each subject. The values of each subjects’ ROI are then averaged to identify the

average value of each relevant ROI. This step returns a csv file with all mean FA values of the new ROIs. The final step in this process uses all ROI files to create a spreadsheet that is used in the analysis. Subjects' meta-data spreadsheet containing relevant covariates are combined with all desired ROIs from individual subject files. It is this file that is used to perform the statistical analysis.

2.5 Analysis

The main analysis of this study focused on relationships of white matter tract integrity and levels of SW. To do this, a regression analysis was performed. Using the individual subjects' FA data, the average FA of the SLF, ATR, IFO, UF, CB, and SCC was calculated. These FA values were regressed against the SW measures acquired by the CAPE. In this analysis, age and sex were controlled for and global FA measures were used as a covariate. The same analysis was performed for MD measures of the white matter tracts.

R Studio was used to create a script to perform these analyses (RStudio Team, 2019). Within this script, three files are used. The first file includes the DTI measures of each subjects' white matter tracts, the second is the CAPE scores, and lastly is a list of possible covariates. The first step of this analysis is to calculate the CAPE factorizations of each participant. This is performed in a separate script but returns the values of CAPE Total score, CAPE Positive score, CAPE Negative score, CAPE Depressive score, and CAPE SW score. To calculate the SW scores, the factor loadings of Ziermans (2013) were used. These consist of .74 for question 3, .84 for question 4, .42 for question 16, and .50 for question 29. By multiplying each question's score by the corresponding loading and then summing them, we were able to quantify each subject's level of SW.

Once the SW score was calculated, the regression was performed. The average FA and MD of each white matter tract was regressed against total CAPE score and the covariates of age, sex, handedness, and IQ. This regression was then be performed again for each tract, however, this time the regression included the CAPE SW score. A second regression was performed identical to the first, but the global covariates were not included. These sets of regressions allowed us to measure any relationship that might exist between the integrity of white matter and CAPE total as well as CAPE SW while accounting for particular global covariates. Although the main focus of this study is the SLF, ATR, IFOF, UF, CB, and SCC, this analysis allowed us to analyze a relationship between CAPE measures and all white matter tracts found in the ENIGMA DTI Pipeline. In order to correct for the number of tests being performed, a Bonferroni correction was used, allowing for the least number of false positives.

3 RESULTS

3.1 Social Withdrawal Results

The results four our SW scores showed a range of 2.5 to 9.58 with the median score being 4.160 and the average being 4.321. There was no association between SW scores and sex, however, there was a significant negative effect of age (unstandardized b = -.0284, β = -.1084; p = .0358) (Figure 1). The range of CAPE Total scores was 42 to 107 with a median score of 62 and an average of 63.28. There was no association between Total scores and sex, but there was a significant negative association between Total scores and age (unstandardized b = -.2369, β = -.1185; p = .0217). SW was also significantly correlated with Total scores (unstandardized b =

.0725; β = .5536; $p < .05$). This relationship remained significant after controlling for age and sex (unstandardized $b = .0712$; β = .5492; $p < .05$).

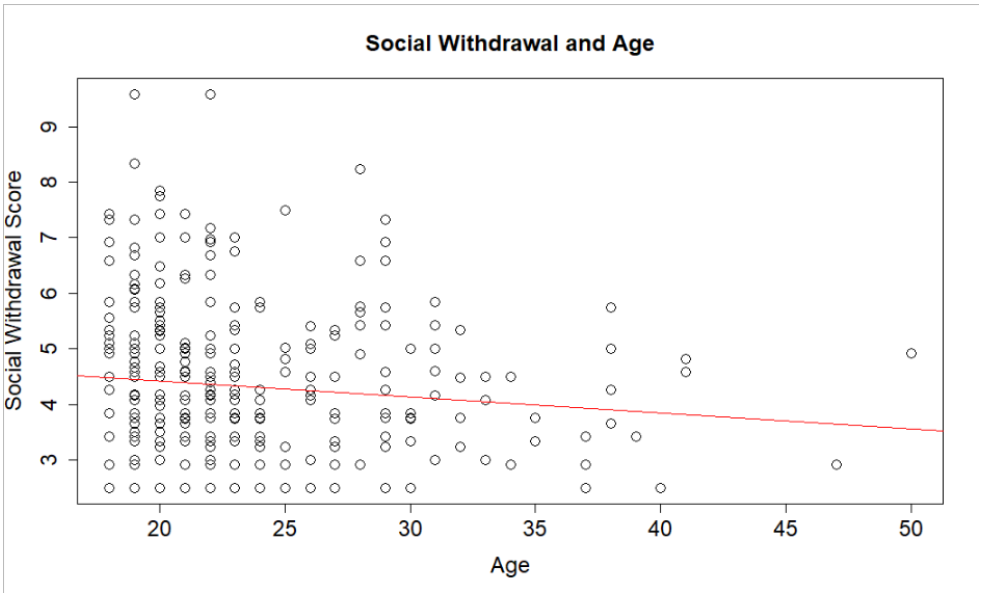

Figure 1 Significant, negative relationship between Social Withdrawal and Age (unstandardized b = -.0284, β = -.1084; p = .0358).

3.2 Fractional Anisotropy Analysis

A regression analysis was performed between FA measures of the SLF, IFOF, UF, CB, and SCC and SW scores with average FA, IQ, sex, and age included as covariates. Neither the SLF, IFOF, UF, CB, nor the SCC had a significant relationship with SW. Further, there was no significant association between these tracts and IQ. It should be noted that the CB (Figure 2) and SCC (Figure 3) did have negative relationships with SW, as was predicted. See Table 2 for a list of all statistical results of the Fractional Anisotropy Analysis. A similar regression was performed with CAPE Total scores; again, no significant relationship was found between these scores and any tract of interest.

Regarding age, the results of this analysis were mixed. The SCC, SLF, UF, and IFOF did not have a significant relationship with age, however, the CB showed a significant, positive association, but this did not survive Bonferroni correction (Figure 4).

Sex had a significant, negative association with tract integrity in the CB (Figure 5A) and SLF, and significant positive association in the SCC (Figure 5B). In this analysis, a negative association would indicate that females had lower FA values compared to males and a positive association indicates that females had greater FA values compared to males. Integrity in the UF and IFOF was not significantly associated with sex.

The same FA analysis was run while excluding IQ as a covariate. This only altered the results slightly as all previous significant findings remained significant and no new significant results were found. For a complete list of statistical results of the Fractional Anisotropy Analysis while excluding IQ, see Table 3.

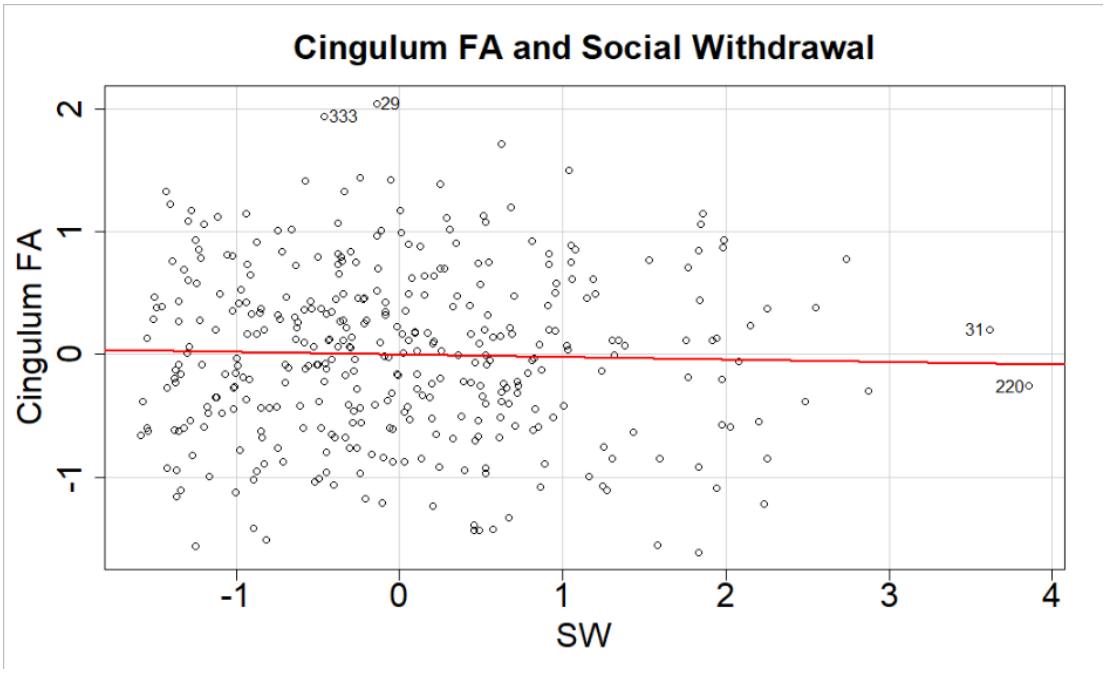

Figure 2 Negative relationship between Cingulum FA and Social Withdrawal (unstandardized b = -.0004, β = -.0196, p = .586). All axes have been scaled to account for other variables included in the model.

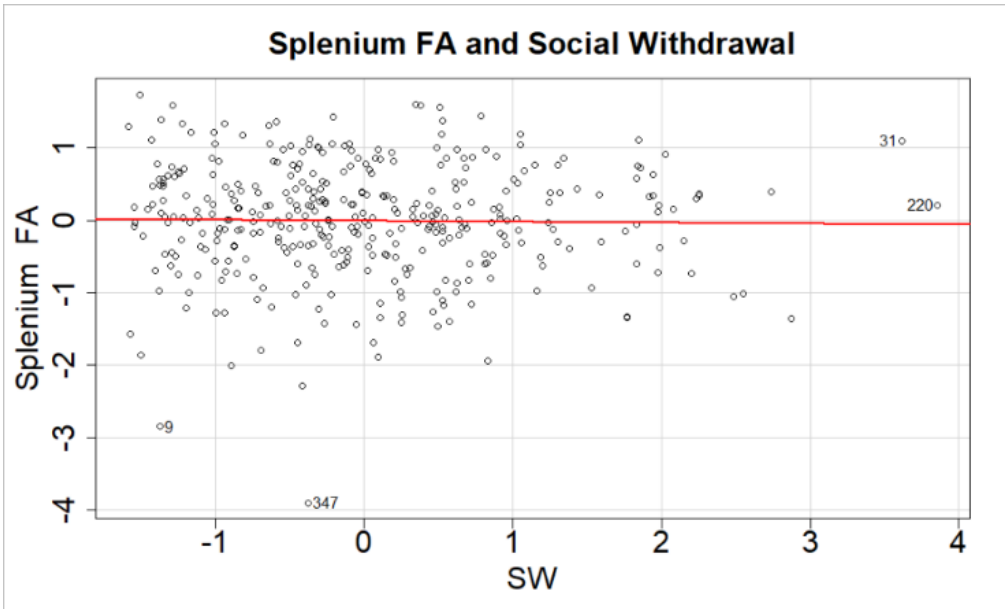

Figure 3 Negative relationship between Splenium of the Corpus Callosum FA and Social Withdrawal (unstandardized b = -.0002, β = -.0137, p = .738). All axes have been scaled to account for other variables included in the model.

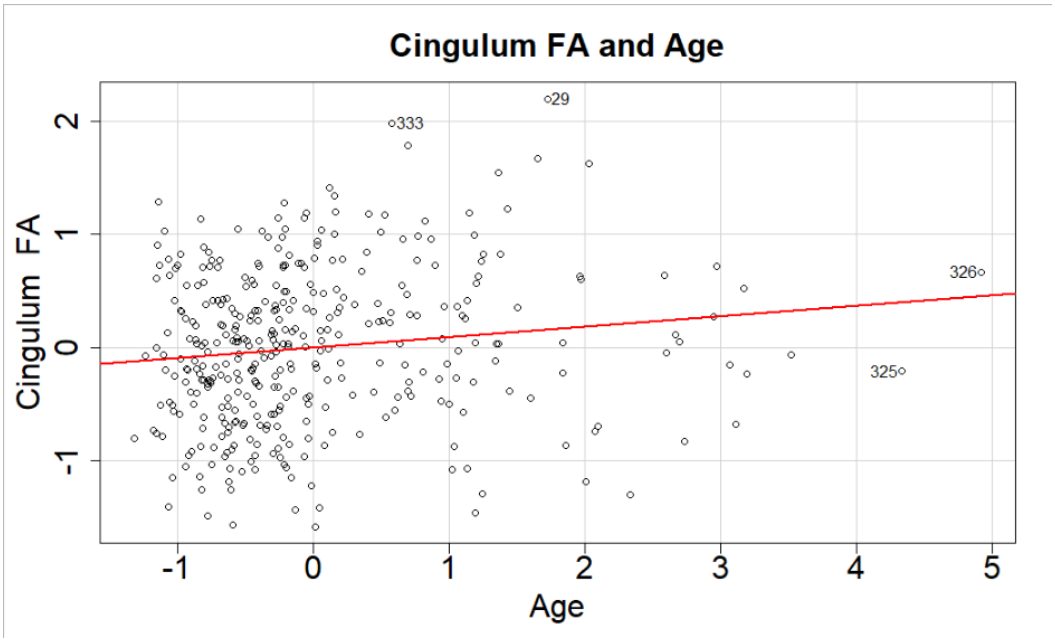

Figure 4 Significant, positive relationship between Cingulum FA and Age (unstandardized b = .0005, β =.0917; p = .012). All axes have been scaled to account for other variables included in the model.

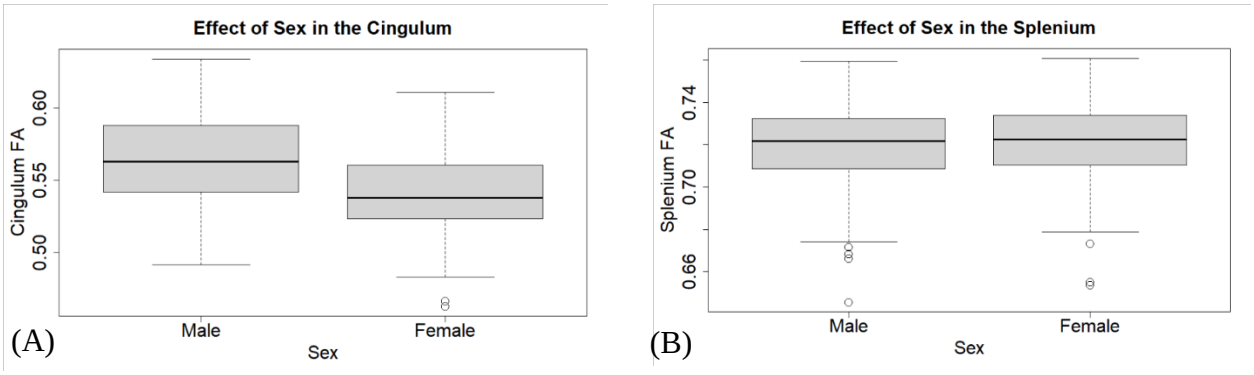

Figure 5 (A) Effect of Sex in Cingulum FA. (B) Effect of Sex in Splenium FA.

Table 2 Fractional Anisotropy Analysis Results. "" represents a significant p-value less than .05.*

Tract	Variable	Unstandardized *b*	β	*P* - Value
SLF	SW	0.0004	0.0261	0.455
	IQ	0.00002	0.0154	0.66
	Age	-0.0001	-0.0319	0.366
	Sex	-0.0040	-0.2171	0.003*
IFOF	SW	0.0013	0.0476	0.305
	IQ	-.0001	-0.0335	0.47
	Age	0.0002	0.0324	0.489
	Sex	0.0029	0.0781	0.417
UF	SW	0.0020	0.0653	0.158
	IQ	-0.0002	-0.0567	0.219
	Age	-.0001	-0.0084	0.857
	Sex	-0.0035	-0.0814	0.395
CB	SW	-0.0004	-0.0196	0.586
	IQ	0.0001	0.0452	0.209
	Age	0.0005	0.0917	0.012*
	Sex	-0.0125	-0.4025	0*
SCC	SW	-0.0002	-0.0137	0.738
	IQ	-.0001	-0.0576	0.159
	Age	-0.0003	-0.0702	0.089
	Sex	0.0074	0.3900	0*

Table 3 Fractional Anisotropy Results while Excluding IQ as a Covariate. "" represents a significant p-value less than .05.*

Tract	Variable	Unstandardized *b*	β	*P* - Value
SLF	SW	0.0004	0.0294	0.398
	Age	-0.0001	-0.0278	0.43
	Sex	-0.0040	-0.2106	0.004*
IFOF	SW	0.0014	0.0523	0.256
	Age	0.0002	0.0342	0.462
	Sex	0.0035	0.0923	0.332
UF	SW	0.0020	0.0607	0.186
	Age	-.0001	-0.0115	0.805
	Sex	-0.0028	-0.0649	0.493
CB	SW	-0.0004	-0.0185	0.603
	Age	0.0005	0.0913	0.012*
	Sex	-0.0128	-0.4128	0*
SCC	SW	-0.0002	-0.0169	0.678
	Age	-0.0003	-0.0732	0.076
	Sex	0.0073	0.3854	0*

3.3 Mean Diffusivity Analysis

The results of our MD analysis were largely similar to those of the FA analysis. Neither the SLF, IFOF, UF, CB, or the SCC had a significant relationship between SW and tract integrity nor was there a significant relationship between either of these tracts and IQ. It should be noted that the SLF (Figure 6), CB (Figure 7), and UF (Figure 8) had expected positive relationships with SW. See Table 4 for a list of statistical results of the Mean Diffusivity Analysis. A similar regression was performed with CAPE Total scores; again, no significant relationship was found between these scores and any tract of interest.

The age effects seen in the MD analysis are much more uniform. The CB (Figure 9), SCC, SLF, and the UF all had significant, positive relationships with age. However, one tract, the IFOF, had a significant, negative association with age (Figure 10).

Sex effects, however, shared mixed results similar to those found in the FA analysis. The CB (Figure 11A) and the IFOF had significant, positive relationships with sex, indicating that women had higher levels of MD in these tracts compared to men. The SCC, SLF (Figure 11B),

and the UF all had significant negative associations with sex, meaning men had higher levels of MD in these tracts than women. The effect of sex in the UF did not survive Bonferroni correction.

The same MD analysis was run while excluding IQ as a covariate. This only altered the results slightly as all previous significant findings remained significant and no new significant results were found. For a complete list of statistical results of the Mean Diffusivity Analysis while excluding IQ, see Table 5.

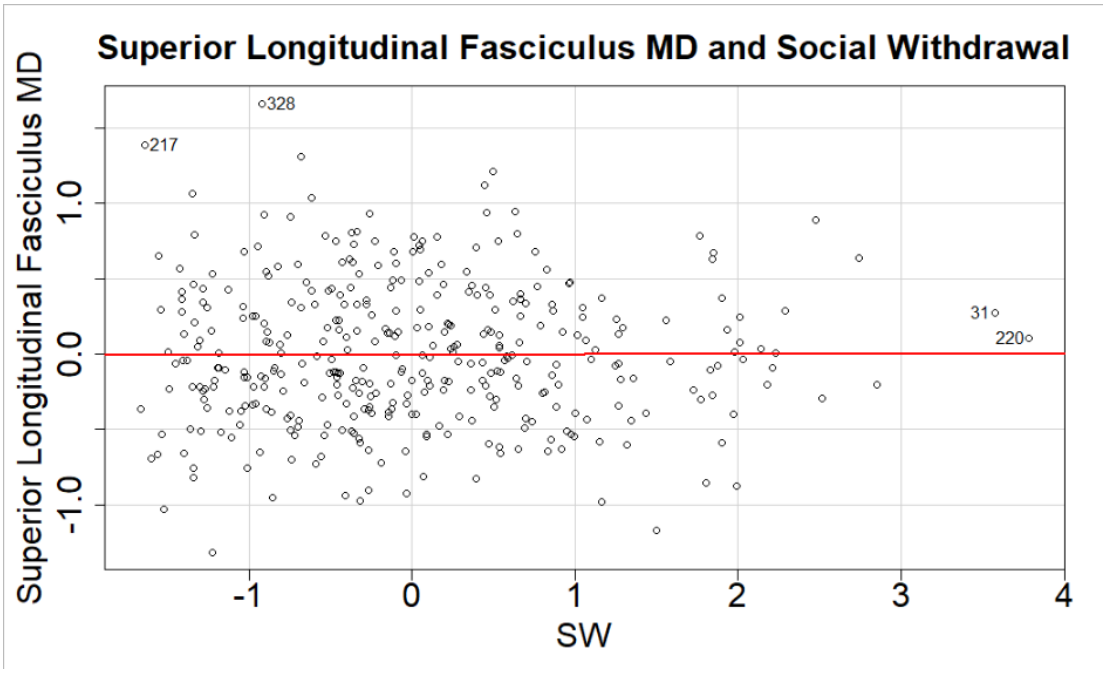

Figure 6 Positive relationship between Superior Longitudinal Fasciculus MD and Social Withdrawal (unstandardized b = 2.02e-8, β = .0019, p = .939). All axes have been scaled to account for other variables included in the model.

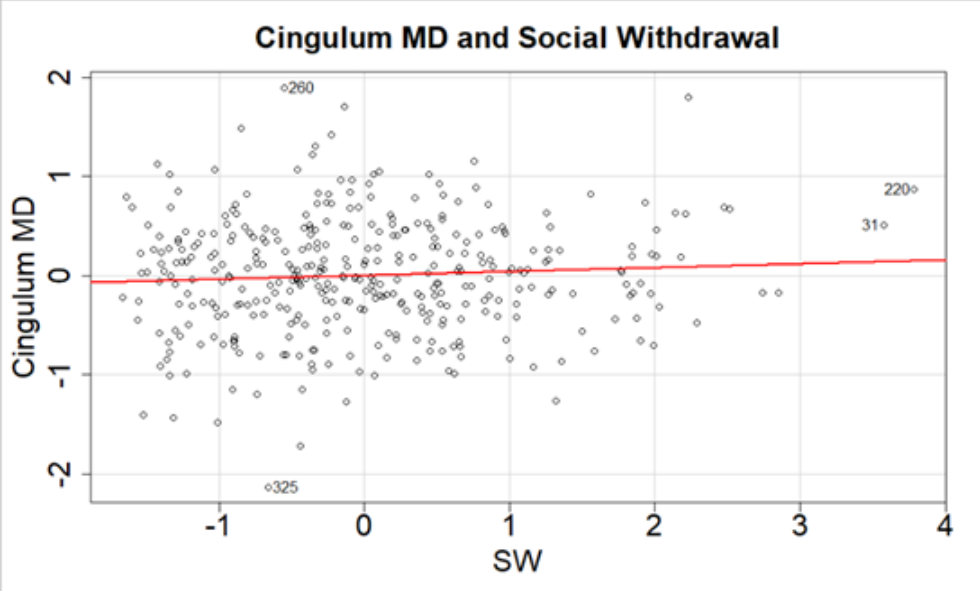

Figure 7 Positive relationship between Cingulum MD and Social Withdrawal (unstandardized b = 4.33e-07, β =.0394, p = .196). All axes have been scaled to account for other variables included in the model.

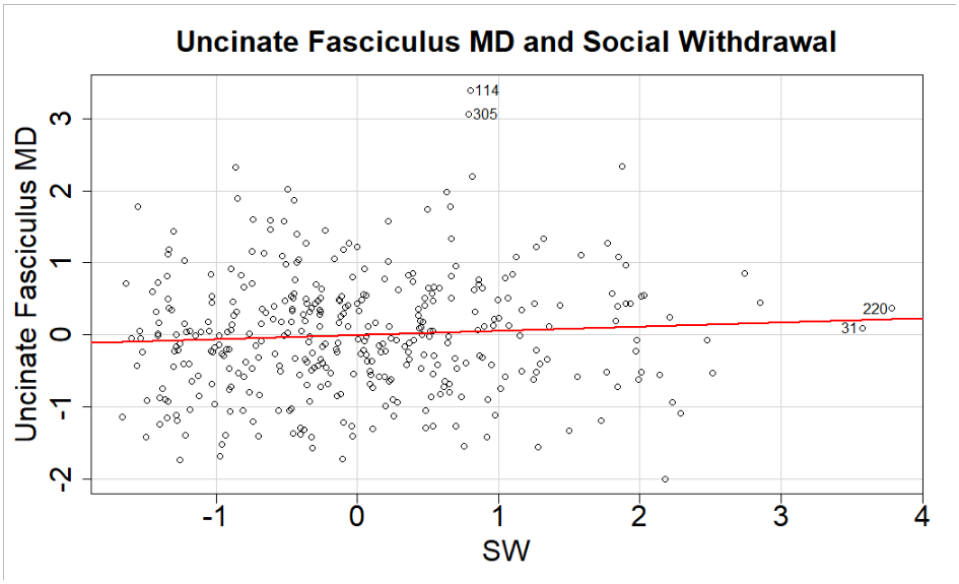

Figure 8 Positive relationship between Uncinate Fasciculus MD and Social Withdrawal (unstandardized b = 1.393e-06, β = .0573, p = .191). All axes have been scaled to account for other variables included in the model.

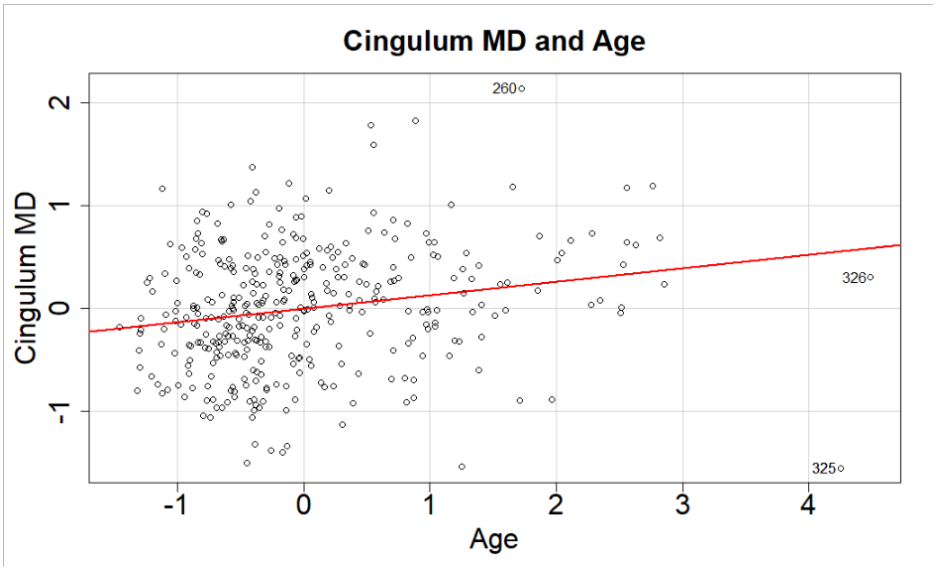

Figure 9 Significant, positive relationship between Cingulum MD and Age (unstandardized b = 3.76e-08, β = .1308, p < .05). All axes have been scaled to account for other variables included in the model.

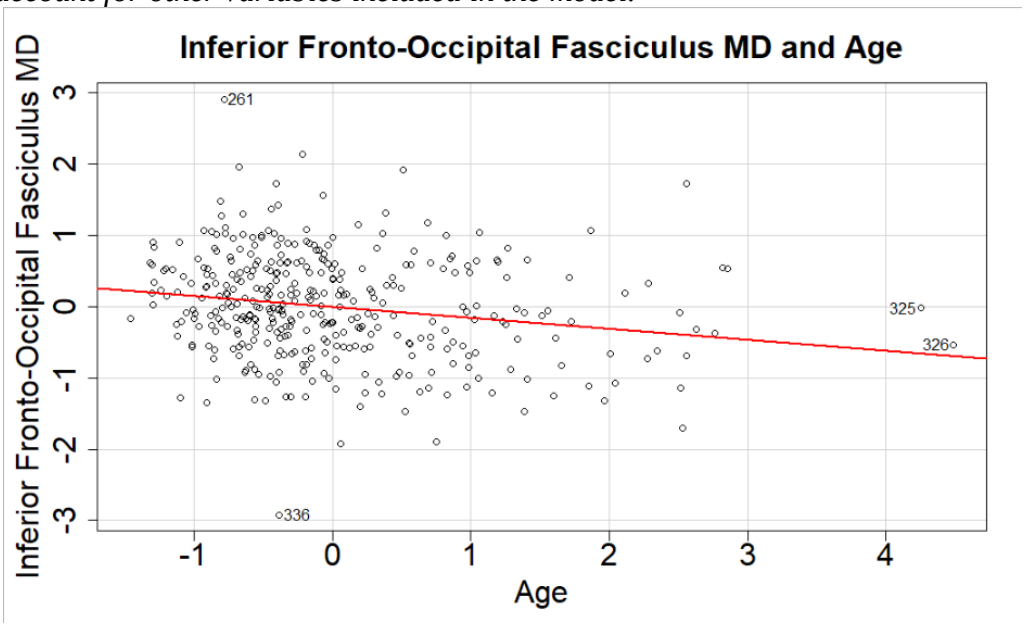

Figure 10 Significant, negative relationship between Inferior Fronto-Occipital Fasciculus MD and Age (unstandardized b = -6.10e-07, β = -.1541, p = <.05). All axes have been scaled to account for other variables included in the model.

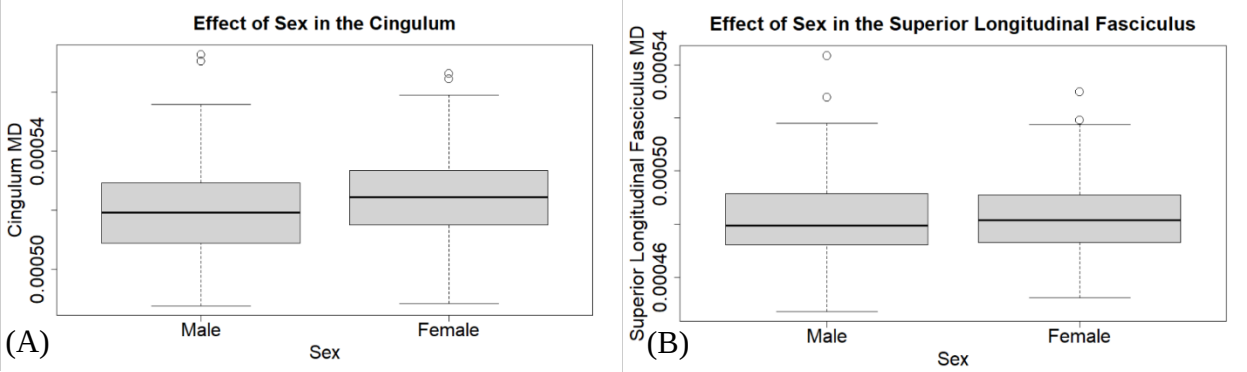

Figure 11(A) Effect of Sex in Cingulum MD. (B) Effect of Sex in the Superior Longitudinal Fasciculus MD.

Table 4 Mean Diffusivity Analysis Results. "" represents a significant p-value less than .05*

Tract	Variable	Unstandardized *b*	β	*P* - Value
SLF	SW	0.00000002	0.0019	0.939
	IQ	-.000000009	-0.0088	0.721
	Age	0.0000004	0.1686	0*
	Sex	-0.000005	-0.3285	0*
IFOF	SW	-0.0000004	-0.0272	0.477
	IQ	0.000000008	0.0051	0.894
	Age	-0.0000006	-0.1541	0*
	Sex	0.000001	0.0576	0.465
UF	SW	0.000001	0.0573	0.191
	IQ	-0.000000002	-0.0008	0.985
	Age	0.000001	0.2583	0*
	Sex	-0.000005	-0.1871	0.038*
CB	SW	0.0000004	0.0394	0.196
	IQ	0.00000004	0.0412	0.175
	Age	0.0000003	0.1308	0*
	Sex	0.0000007	0.0521	0.407
SCC	SW	-0.0000005	-0.0461	0.261
	IQ	-0.00000004	-0.0353	0.388
	Age	0.0000004	0.1363	0.002*
	Sex	-0.000004	-0.2629	0.002*

Table 5 Mean Diffusivity Analysis Results while Excluding IQ as a Covariate. "" represents a significant p-value less than .05*

Tract	Variable	Unstandardized *b*	β	*P* - Value
SLF	SW	0.00000004	0.0037	0.882
	Age	0.0000005	0.1676	0*
	Sex	-0.000005	-0.327	0*
IFOF	SW	-0.0000004	-0.0259	0.493
	Age	-0.0000006	-0.1554	0*
	Sex	0.000001	0.0573	0.459
UF	SW	0.000001	0.0586	0.176
	Age	0.000002	0.2573	0*
	Sex	-0.000006	-0.1855	0.037*
CB	SW	0.0000004	0.0376	0.213
	Age	0.0000004	0.1287	0*
	Sex	0.0000006	0.0368	0.552
SCC	SW	-0.0000005	-0.0458	0.26
	Age	0.0000004	0.1361	0.002*
	Sex	-0.000004	-0.254	0.002*

4 DISCUSSION

Based on previous literature discussed above, we expected the FA of our tracts of interest to be negatively associated with SW and for MD to be positively associated. We did not find any significant relationship between any tracts and SW in either the FA or MD analysis. The IFOF, UF, and SLF were selected because they had previously been implicated in interpersonal schizotypy, but this may be the extent of their role (Pfarr & Nenadić, 2020). SW is a specific personality trait that is found in schizotypy, and not necessarily equivalent to the entire interpersonal dimension. The tracts included in this analysis may influence the broader aspects of social function in schizotypy, but not the particular trait of withdrawing from society and social activities. In other words, general healthy social functioning may be reliant on healthy IFOF, UF, and SLF, but they do not affect someone's willingness to take part in social activities, interact with others, and create new relationships. This social trait may be connected to separate tracts.

Two of our tracts, the CB and SCC, did show the predicted negative association between FA and SW while the others were positive. These two tracts have not been connected to

interpersonal schizotypy but have been shown to influence social cognition (Herbet et al., 2014; Kelly et al., 2018; Knyazeva, 2013; Wu et al., 2016). As such, these results suggest that further analysis of these two may be beneficial to uncovering driving forces of social deficits in schizotypy. As for the MD analysis, the SLF and UF had the predicted positive association with SW, which is in line with previous findings of Pfarr and Nenadić (2020) and indicate that these two may be implicated in this personality trait. Again, we saw the predicted association between CB MD and SW, further evidence that this tract should be studied in more detail. Other tracts have been found to be involved in social functioning, such as the fornix, but were not included in this analysis as they did not come up in previous schizotypy literature. The CB and SCC were included because of previous findings connecting them to social cognition. It could be that other tracts which have not yet been implicated in schizotypy may have some role in SW and should be included in similar analyses.

We did not have a specific hypothesis regarding age and sex, but both were included in our model to make sure that they were taken into account. Our results regarding age and SW scores reflect what would be expected of social function in someone within our age range. The impact of social activities such as school, work, and raising children would likely influence someone to become more socially involved with the world around them. In terms of DTI values, FA should decrease with age and MD should increase as it indicates a worsening of tract integrity (Sullivan et al., 2010). More specifically, FA typically increases and reaches peak values between 23 and 39 years of age while MD has an inverse trend (Kochunov et al., 2012; Yap et al., 2013). From mid-adulthood to old age however, tract integrity typically declines, signified by a decrease in FA values and an increase in MD values (Yap et al., 2013). Given the ages of our sample range from 18 to 50 years old with an average of 22, we are in this peak

range, which may be the reason for such varying findings in both our MD and FA results. The FA analysis shows that the integrity of the CB increased with the age of our sample which should be occurring based on previous findings. As the sample increases with age, white matter should mature, resulting in completely formed tracts. Our MD analysis seems to show the opposite in that the majority of the tracts' MD increased with age, indicating a reduction in integrity.

As for sex effects on DTI values, there is evidence that FA and MD values can differ in certain tracts between men and women (Inano et al., 2011; Sullivan et al., 2010). FA was found to be higher in men in the CB, SLF, and SCC while FA was lower in women in the column of the fornix (Inano et al., 2011). Our FA results in the CB and SLF are similar to these but that is not the case in the SCC. Our results in the MD analysis are also mixed and do not follow previously found trends in the CB, SLF, and SCC. As mentioned above, this sample's age range is a plateau for WM with many tracts reaching their maturity, however, it has been shown that these tracts reach their peaks at different ages. For example, the SLF has been shown to peak around 29 years of age, the SCC around 34, and the CB around 40 (Kochunov et al., 2012). This may be the reason that we do not see uniform results for age and sex as the tracts themselves may be at different levels of maturity and therefore, varying levels of integrity as measured by FA and MD. This could be the reason for the mixed findings of FA and MD in age and sex.

5 LIMITAIONS

The reason for these results is unclear, but there are many aspects of this study that could have contributed. First, this study only included FA and MD, which are commonly used in DTI analyses, but by excluding RD and AD, we are missing part of the picture as these measures are not independent (Alexander et al., 2011; O'Donnell & Westin, 2011). First, RD and AD are

considered to be more direct measures of WM dimensions with RD reflecting myelination and AD reflecting a variety of WM alterations such as injury (Alexander et al., 2011). Further, the equations for both FA and MD rely upon all measured eigenvalues, the largest of which is equal to AD (O'Donnel & Westin, 2011). RD and AD have also been shown to affect FA and MD measures and including them in an analysis will help to better understand associations between DTI measures and scale measurements (Alexander et al., 2011; O'Donnell & Westin, 2011; Vos et al., 2011). Clearly, these two measures may offer more insight into tract integrity than just FA and MD alone. Including RD and AD may offer a clue as to why we did not see the expected relationships between FA, MD, and SW. It could be possible that either of these two DTI measures are associated with SW in a way that FA and MD are not. By incorporating these measures and expanding our tracts of interest to include those which are known to be connected with general social functioning, we will be able to create a better picture of the neural underpinnings of SW personality traits in schizotypy.

On the topic of previous schizotypy research, the studies discussed in this paper used the Schizotypal Personality Questionnaire (SPQ) to measure schizotypy severity while our sample was measured using the CAPE. This adds another layer to our limitations as the CAPE's measures may not align with those of the SPQ, which could ultimately affect the associations between tract integrity and social function. It's possible that we did not see associations similar to those of previous literature because our scale did not properly measure SW. Although both scales are used to measure severity of schizotypy traits, they do have their differences.

The CAPE was originally developed to include more robust measures of depression as it was seen to influence the expression of positive and negative psychosis experiences (Stefanis et al., 2002). Depression scales were not included in the SPQ, which may be a reason for such

different results between our study and previous research. Further, the CAPE does not include items that measure SW directly. Instead, we had to use a SW factor that only a few studies have found (Mark & Toulololoulou, 2016; Schlier et al., 2015; Ziermans, 2013). This scale includes only 14 items that could possibly measure social personality and of these 14 only 4 are included in the factor. On the other hand, the SPQ offers 25 items from three subscales, "No Close Friends," "Extreme Social Anxiety," and "Constricted Affect," that reflect a social aspect close to social withdrawal (Fonseca-Pedrero et al., 2018; Gruzelier, 1996; Zhang & Brenner, 2017). The SPQ could offer a much better measure of social personality deficits within a schizotypy population and therefore should be used in future analyses of SW personality traits. Including multiple schizotypy scales and harmonizing the scores might create an even more reliable measure of social function.

Lastly, Tract Based Spatial Statistics (TBSS) is often used for analyzing DTI data and is a cornerstone of the ENIGMA DTI pipeline, but it is not perfect (Bach et al., 2014; Jahanshad et al., 2013; Kochunov et al., 2014). The ENIGMA DTI working group created a new DTI template to which all FA images are registered when following ENIGMA DTI protocols. This registration step is performed using TBSS. Differences in registration techniques have been shown to alter DTI results, and therefore this step should be considered when analyzing the results of a DTI analysis (Bach et al., 2014). In fact, TBSS has been shown to improperly assign FA values to the correct tract and in some cases the values of one tract may include more than 10 percent of diffusion measurements from another (Bach et al., 2014). That is to say that, when using TBSS for registration techniques, DTI values assigned to a specific tract like the CB may not have been calculated using data found in that tract alone and may be influenced by nearby voxels (Bach et al., 2014; Schwarz et al., 2014). This uncertainty between tracts is due to TBSS's use of only FA

maps and disregard for full tensor information, including fiber orientation (Bach et al., 2014; Mishra et al., 2019). This creates problems in being able to differentiate between two anatomically close regions (Bach et al., 2014; Schwarz et al., 2019).

However, another registration approach, DTI-TK, does incorporate full tensor information including orientation (Bach et al., 2014; Mishra et al., 2019). By replacing the TBSS registration step with that of DTI-TK, Bach et al. (2014) found that misassignment of DTI values was reduced by a factor of 7 while Mishra et al. (2019) found DTI-Tk to be more sensitive to DTI measures. In comparing DTI-TK to FA based registration techniques, Keihaninejad et al. (2013) found DTI-TK to have more consistent measures. When performing multiple scans, back-to-back, the DTI-TK had very low FA differences between scans while FA based techniques showed significant differences between scans (Keihaninejad et al., 2013). TBSS is the standard when it comes to DTI analyses, but it is not perfect. DTI-TK has been shown to be able to improve the problems with anatomical specificity that may arise with this approach. By replacing the TBSS registration step with DTI-TK, future studies may be able to produce more reliable and accurate DTI measures.

6 CONCLUSION

Based on the results of this analysis, it can be concluded that there is no significant relationship between tract integrity of the CB, IFOF, SCC, SLF, and UF, as measured by either FA or MD, and SW severity as measured by the CAPE. It is possible that these tracts may not be related to SW specifically, but instead contribute to the more general interpersonal dimension of schizotypy and go no further than that. Other tracts that have been implicated in general social cognition could play a role in SW. Therefore, it is imperative that similar analyses expand to include these tracts, RD and AD measures, as well as the SPQ.

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