White Matter Correlates of Psychosis-Linked Traits Support Continuity Between Personality and Psychopathology

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The link between diagnoses of psychotic disorders and attenuated white matter connectivity is well established, but little is known about the degree to which similar white matter differences predict traits linked to psychosis-proneness in the general population. Moreover, intelligence is too rarely considered as a covariate in neural endophenotype studies, despite its known protective role against psychopathology in general and its associations with broad aspects of neural structure and function. To determine whether psychosis-linked personality traits are linearly associated with white matter microstructure, we examined white matter correlates of Psychoticism, Absorption, and Openness to Experience in a large community sample, covarying for sex, age, and IQ. Findings support our hypothesis that the white matter correlates of the shared variance of these traits overlap substantially with the frontal lobe white matter connectivity patterns characteristic of psychotic spectrum disorders. These findings provide biological support for the notion that liability to psychosis is distributed throughout the population, is evident in brain structure, and manifests as normal personality variation at subclinical levels.

General Scientific Summary
This study demonstrates that regionally specific white matter coherence patterns typically linked to psychotic spectrum liability are associated with positive schizotypy and Openness to Experience in a large community sample. These findings suggest that individual differences in frontal and temporal white matter may underpin nonclinical expressions of psychosis-linked personality traits.

Keywords: DTI, psychosis, schizotypy, personality, intelligence

Psychosis is a broad term that describes loss of contact with reality marked by delusions and hallucinations. Psychotic spectrum illnesses such as schizophrenia and bipolar disorder are common, highly heritable (60–80%), developmental disorders that confer significant personal and societal costs (Ripke et al., 2014). Enormous efforts have been made to understand the etiology of psychotic spectrum disorders, but most studies use case-control designs with categorical criteria for health and disease. Recent evidence from psychometric and genetic research in large samples indicates that latent risk for psychosis is not categorical but instead is expressed as a dimensional likelihood of experiencing aberrant interpretations of reality, with severity differing on a continuum between health and illness (Bigdeli et al., 2014; Kendler, 2015; Purcell et al., 2014; Ripke et al., 2014). This emerging picture points to two important goals for individual differences research: (a) to identify nonclinical traits that comprise expressions of underlying biological risk (often described broadly as “schizotypy”) and (b) to examine the extent to which these traits are associated with neurobiological changes that overlap with the “dysconnectivity” typically observed in psychotic spectrum disorders (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011).

The continuum model of psychosis proneness is based on evidence for an “extended psychosis phenotype” (Van Os & Linscott, 2012). In several studies assessing general population samples, the severity and temporal stability of psychosis-linked cognitive–behavioral vulnerability markers predict later psychosis (e.g., Debbane et al., 2014; Kwapił, Gross, Silvia, & Barrantes-Vidal, 2013). The continuum model also suggests that features of neurobiological variation related to psychotic disorders (e.g., white matter
microstructure) are likely to be identifiable as endophenotypes that (a) reflect degree of latent genetic risk and (b) are linearly associated with cognitive–behavioral manifestations of psychosis-proneness. These cognitive–behavioral manifestations (i.e., traits) are multidimensional, and the most commonly studied multidimensional construct in psychosis-proneness research is schizotypy.

Schizotypy typically refers either to liability for schizophrenia-spectrum disorders or to a trait reflecting subclinical levels of the symptoms of these disorders. These two conceptions are compatible because higher levels of the trait increase the risk of disorder. Some disagreement persists regarding the precise factor structure of schizotypy, but many analyses show that it primarily comprises three factors, which broadly correspond to the positive, negative, and disorganized symptoms of schizophrenia (Fonseca-Pedrero et al., 2008; Wuthrich & Bates, 2006). Positive schizotypy includes magical ideation, unusual beliefs, perceptual aberration, and over-inclusive thinking, whereas negative schizotypy includes physical and social anhedonia (lack of pleasure in social and sensory experience; Kwapil, Barrantes-Vidal, & Silvia, 2008; Ross, Lutz, & Bailley, 2002). The third factor, cognitive disorganization, is less well established than the other two but includes erratic behavior and speech as well as cognitive deficits, such as impaired working memory (Goghiari, Sponheim, & MacDonald, 2010; Kwapil et al., 2008). Paranoid tendencies appear to load approximately equally on positive and negative schizotypy (Wuthrich & Bates, 2006).

Results from diverse areas of schizotypy research demonstrate the utility of assessing the different symptom dimensions separately when investigating the associations between schizotypy and psychological or biological criteria, including creativity, neuromaging measures, and even longitudinal prediction of psychosis conversion (e.g., Hori et al., 2014; Katagiri et al., 2015; Nettle, 2006; Ross et al., 2002). These studies point to the existence of distinct etiological underpinnings for the separable schizotypy dimensions, especially for positive versus negative symptoms (Katagiri et al., 2015). (Because the diagnostic criteria for schizotypal personality disorder underrepresents positive relative to negative symptoms, we do not discuss research on the correlates of this diagnosis; Tackett, Silberschmidt, Krueger, & Sponheim, 2008).

The core of expressed genetic liability for psychosis (across multiple disorders involving psychosis) is captured well by positive schizotypy but not by negative or disorganized schizotypy, and models of additive genetic effects contributing to positive schizotypy indicate that this liability is fully dimensional (Bigdeli et al., 2014; Grant, Munk, Kuepper, Wielpuetz, & Hennig, 2015; Kwapil & Barrantes-Vidal, 2015). A study of the association between schizotypy dimensions (positive, negative, and disorganized) and later development of clinically significant mental illness, in four independent, general-population samples (total N = 7,282), found that only positive schizotypy scores were associated with development of a psychotic disorder (Debbane et al., 2014).

Of note, at least two studies that selected participants based on an extreme-groups design demonstrated links between negative schizotypy scores and psychotic-like symptoms (Kwapil, Crump, & Pickup, 2002; Kwapil et al., 2013). However, follow-up analysis in the 2013 study demonstrated that the prospective risk of negative schizotypy did not hold after correction for sample selection using extreme groups (Kwapil et al., 2013). Consistent with this finding, several studies examining schizotypy in community samples found that negative schizotypy was specifically linked to nonpsychotic schizophrenia symptoms, such as anhedonia and social avoidance, but did not independently contribute to risk for psychosis when controlling for positive schizotypy (Barrantes-Vidal et al., 2013; Barrantes-Vidal, Lewandowski, & Kwapil, 2010; Kwapil, 1998). Taken together, these findings emphasize the importance of examining the distinct etiology of the positive schizotypy dimension (and related traits) in clinical and nonclinical samples.

Psychosis-Proneness and the Big Five

Given the evidence that dysfunctional traits, such as positive schizotypy, tend to be variants of normal traits, it is crucial to unify models of normal and abnormal trait expression—not as categorical differences, but as continuous underlying variables reflecting differences in propensities to experience psychopathology (Krueger & Markon, 2006; Widiger & Trull, 2007). To this end, we draw upon findings that support the incorporation of positive schizotypy with the Five-Factor Model of personality or the “Big Five.” The Big Five personality factors constitute a reasonably comprehensive description of the most important dimensions of human individual differences in normal and abnormal personality traits (John, Naumann, & Soto, 2008; Krueger & Markon, 2014; Markon, Krueger, & Watson, 2005).

The Big Five dimension most often hypothesized to relate to positive schizotypy is Openness/Intellect (O/I), which encompasses a broad domain of traits including imagination, intellectual interests, curiosity, creativity, aesthetic interests, and unconventionality (DeYoung, 2015; DeYoung, Grazioplene, & Peterson, 2012). As suggested by the compound label, this domain contains two distinct subfactors: Openness to Experience (henceforth “Openness”) and Intellect. Although they are positively correlated, these two aspects of the broader Big Five trait have importantly different external correlates (DeYoung, 2015; DeYoung et al., 2012; DeYoung, Quilty, & Peterson, 2007). Both aspects of O/I reflect the tendency to explore the world cognitively, but Intellect reflects individual differences in the propensity to engage with abstract or semantic information (descriptors include “intellectual,” “clever,” and “philosophical”) whereas Openness reflects individual differences in the propensity to engage with perceptual or sensory information (“perceptive,” “artistic,” “fantasy-prone”).

Considerable controversy has been generated by the question of whether positive schizotypy can be considered a maladaptive variant of O/I. This is largely because measures of positive schizotypy are sometimes more strongly correlated with Neuroticism than with O/I, and they sometimes form a separate, sixth factor, if six rather than five factors are extracted (Ashton, Lee, de Vries, Hensrickse, & Born, 2012; Watson, Clark, & Chmielewski, 2008). Nonetheless, many studies have found that when only five factors are extracted, positive schizotypy falls in the same factor as O/I (Ashton et al., 2012, footnote 6; Gore & Widiger, 2013; Markon et al., 2005, Study 2; Thomas et al., 2013; Watson, Clark, & Chmielewski, 2008). Item response theory (IRT) studies have come to conflicting conclusions about whether items measuring O/I and positive schizotypy are assessing the same latent dimension (Stepp et al., 2012; Suzuki, Samuel, Pahlen, & Krueger, 2015).
We believe that the difficulty in reaching consensus regarding the relation of positive schizotypy to O/I stems mostly from the fact that the Openness and Intellect subfactors are differentially related to positive schizotypy. Research in clinical and healthy populations has shown that the Openness aspect of O/I is positively related to positive schizotypy whereas the Intellect aspect is either weakly or negatively related to positive schizotypy (Chmielewski, Bagby, Markon, Ring, & Ryder, 2014; DeYoung, Carey, Krueger, & Ross, 2016; DeYoung et al., 2012). A negative association of Intellect with positive schizotypy is consistent with the fact that O/I is the Big Five trait most related to intelligence because the O/I association with intelligence is driven by Intellect rather than Openness (DeYoung, Quilty, Peterson, & Gray, 2014).

Intelligence serves as a protective factor against psychopathology in general and schizophrenia in particular (Gale, Batty, Tynelius, Deary, & Rasmussen, 2010; Zammit et al., 2004). On the basis of all of these findings, we recently proposed a model in which positive schizotypy is described as a variant or facet of Openness specifically (DeYoung, 2015; DeYoung et al., 2012).

What Openness and positive schizotypy share is an elevated tendency to perceive patterns and meaning in loosely related stimuli. In positive schizotypy this tendency is taken to an extreme in which patterns may be identified as objectively real even when they are not (a phenomenon also known as “apophenia”). Intelligence may play a key role in determining whether identification of patterns by people high in Openness leads to adaptive cognitive abilities—such as creativity, which is strongly linked to Openness (DeYoung, 2015; Kaufman et al., 2016)—or to the apophenia that characterizes positive schizotypy. If this model is accurate, then variation in neurobiological endophenotypes linked to psychosis should be associated with the variance that Openness shares with positive schizotypy, and such effects should be particularly evident when controlling for intelligence.

Broadly speaking, neurostructural and neurofunctional findings indicate that psychotic-spectrum diseases are linked to disrupted or aberrant patterns of neural connectivity. This body of evidence has led to the dysconnectivity theory of psychosis, which states that the core symptoms of psychosis are the result of altered connectivity between brain regions, particularly between specific thalamocortical and frontotemporal regions (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Connectivity is typically observed as aberrantly low in these regions (hypoconnectivity), although some specific interconnections may be aberrantly high (hyperconnectivity; e.g., Filippi et al., 2014). Such altered connectivity patterns are thought to lead to abnormal sensory and cognitive integration (Pettersson-Yeo et al., 2011).

The present study investigated the white matter correlates of Openness and positive schizotypy. This research builds on the work of Jung, Graziozzi, Caprihan, Chavez, and Haier (2010), who examined whole-brain white matter correlates of a creativity test and O/I (as measured by the NEO-Five Factor Inventory, which does not separate Openness and Intellect) while controlling for IQ. This study identified frontothalamic and frontotemporal regions of white matter in which fractional anisotropy (FA; a measure of white matter microstructure) was inversely associated with O/I and reported that these regions display a “surprising” degree of anatomical overlap with white matter reductions prototypically seen in psychotic spectrum disorders (Jung et al., 2010). Specifically, these findings overlap with a region that one meta-analysis of white matter in schizophrenia has called a “hub” region in the deep frontal white matter (Ellison-Wright & Bullmore, 2009). Reduced connectivity in this region is evident early in disease progress (Canu, Agosta, & Filippi, 2015; Filippi et al., 2014; Samartzis, Dimas, Fular-Poli, & Kyriakopoulos, 2014) and is found in first-degree relatives and other high-risk groups (Arat, Chouinard, Cohen, Lewandowski, & Öngür, 2015; Katagiri et al., 2015). The effect has been described as emanating from a centroid roughly at the anterior terminus of the internal capsule. This hub-like region is traversed by several major white matter tracts: the uncinate fasciculus (frontotemporal), the anterior thalamic radiation (frontothalamic), the genu/forceps minor of the corpus callosum (frontal interhemispheric pathways), and the lateral fasciculi (frontoparietal, fronto-occipital; Canu et al., 2015; Ellison-Wright & Bullmore, 2009; Filippi et al., 2014; Skudlarski et al., 2013). Recent studies also support the presence of regional decreases in white matter connectivity in samples that are at “ultra-high risk” or “clinical high risk” for psychosis in frontothalamic white matter (Cho et al., 2016; Katagiri et al., 2015). In general, the evidence for frontal white matter FA reductions associated with severity on the psychosis continuum is highly consistent (compared with the replicability of other brain regions), and FA decreases are the most severe and widespread in patients meeting clinical criteria for psychosis (Carletti et al., 2012; Cho et al., 2016; Katagiri et al., 2015; Skudlarski et al., 2013). Finally, at least one study has identified regions of hyperconnectivity in first-episode unmedicated psychosis, but the regions displaying hyperconnectivity in patients were not overlapping with deep frontal white matter (Filippi et al., 2014).

Although the findings of Jung et al. (2010) linking O/I to reduced FA are intriguing, two similar studies have not found associations between O/I and reduced white matter coherence in community samples (Bjørnebekk et al., 2013; Xu & Potenza, 2012). In the present study, we addressed several of the potential reasons for inconsistency in this area. First, we separated Openness from Intellect, with the hypothesis that only Openness should be negatively associated with FA. Second, we used a measure of positive schizotypy as well as multiple measures of Openness so that we could identify variance in Openness that is shared with positive schizotypy. Third, we controlled for IQ, which was not done in either of the studies that failed to replicate the findings of Jung et al. (2010). Bjørnebekk et al. (2013) included IQ as a covariate only in follow-up analyses of significant effects, which did not include any O/I effects. Controlling for IQ is important because O/I scales are often correlated with IQ and because studies in healthy samples have demonstrated a positive association between IQ and FA that is broadly distributed across major white matter pathways (Chiang et al., 2009; Navas-Sánchez et al., 2014; Penke et al., 2012).

On the basis of previous findings, we hypothesized that there would be an inverse association between FA in frontal lobe white matter and trait scores capturing the shared variance of Openness and positive schizotypy. We also hypothesized that IQ would display positive associations with FA across broad and diffuse white matter regions. In addition to standard measures of Openness and positive schizotypy, we also included the Absorption scale from the Multidimensional Personality Questionnaire (MPQ; Tellegen & Waller, 2008) as another measure of this factor. The full name of the construct measured by this scale is “Openness to...
Absorbing and Self-Altering Experiences” (Tellegen & Atkinson, 1974), indicating its conceptual similarity to Openness to Experience. Factor analyses indicate not only that it is a reasonably good marker of O/I generally, but also that it is a particularly good marker of the Openness subsfactor specifically, especially when modeling the variance that Openness shares with positive schizotypy (DeYoung et al., 2012).

Method

Participants

Analyses were conducted in a sample of psychiatrically healthy, right-handed participants aged 20–40 years (preexclusion N = 264) recruited via CraigsList in Minneapolis-St. Paul, Minnesota. Subjects were screened over the phone by research assistants during study recruitment for current use of psychotropic medications (antipsychotics, anticonvulsants, and stimulants) as well as for history of neurologic or psychiatric disorders and for current drug or alcohol problems. The University of Minnesota Institutional Review Board approved the study, and participants provided written informed consent.

For diffusion-weighted imaging (DWI) analysis, 233 subjects were retained (109 female, mean age = 26 years, SD = 4.9). Five were excluded because they did not complete the behavioral session, 23 were excluded based on excessive head motion (based on visual inspection of motion artifacts, such as blurring or motion warping), and 3 were excluded because of the presence of scanner artifacts (Soares, Marques, Alves, & Sousa, 2013).

Self-Report Questionnaires

Openness and Intellect were assessed using the Big Five Aspect Scales (BFAS), which measure a level of personality structure between the broad Big Five and their many facets (DeYoung et al., 2007), using 100 items rated on a 5-point Likert scale. The BFAS measures an empirically derived substructure of the Big Five, meaning that the two aspects of each Big Five domain are likely to reflect important distinctions for discriminant validity within each domain. The Openness scale from the BFAS includes 10 items such as “See beauty in things that others might not notice” and “Seldom daydream” (reversed), whereas the Intellect scale includes 10 items such as “Am quick to understand things” and “Avoid philosophical discussions” (reversed). Intellect was used as a covariate in all regressions examining associations with Openness because of its differential association with positive schizotypy (DeYoung et al., 2012).

The Absorption scale from the MPQ includes 34 items (α = .90), including, “I can lose contact with reality watching a beautiful sunset,” “At times I somehow feel the presence of someone who is not physically there,” and “I think I really know what some people mean when they talk about mystical experiences” (Tellegen & Waller, 2008). Absorption was measured with the same 5-point scale as the BFAS.

Positive schizotypy was assessed using the Psychoticism scales from the Personality Inventory for DSM–5 (PID-5; Krueger, DeRinger, Markon, Watson, & Skodol, 2012), which measures the maladaptive traits listed in Section III of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM–5). The PID-5 includes 220 items measuring 25 facets of personality disorder organized into five domains: Negative Affectivity, Detachment, Antagonism, Disinhibition, and Psychoticism. These domains appear to represent dysfunctional variants of the Big Five, and several studies have found that Psychoticism aligns with O/I in factor analysis (De Fruyt et al., 2013; Gore & Widiger, 2013; Thomas et al., 2013). Each facet is measured by 4–14 items. PID-5 items are rated on a 4-point scale ranging from “very false or often false” to “very true or often true.” Accumulating evidence supports the construct validity of the PID-5 as a broad measure of psychopathological traits (Krueger & Markon, 2014) The three facets of Psychoticism are Unusual Beliefs and Experiences (e.g., “I believe that some people can move things with their minds”), Eccentricity (e.g., “People have told me that I think about things in a really strange way”), and Perceptual Dysregulation (e.g., “Things around me often feel unreal, or more real than usual”), and they were averaged to yield overall Psychoticism scores.

Although we did not administer any scales specifically designed to measure negative schizotypy symptoms, we used a composite of four facets from the PID-5 to create a Negative Symptom proxy to examine how specific our findings were to traits involved in positive schizotypy. On the basis of the findings of structural analyses describing the associations between the Minnesota Multiphasic Personality Inventory (MMPI)-2-RF and the PID-5 (Anderson et al., 2015), as well as links between PID-5 facets and schizoid personality disorder (Anderson, Snider, Sellbom, & Hopwood, 2014), we created a Negative Symptom score by averaging Intimacy Avoidance, Restricted Affectivity, Withdrawal, and Anhedonia.

Four subjects with high-quality magnetic resonance imaging (MRI) data were missing all PID-5 data because of a computer error. To include these four subjects, Psychoticism and Negative Symptom scores were imputed based on a linear model predicting PID-5 Psychoticism scores from a model including all 10 BFAS scales, MPQ Absorption, and IQ. (Excluding these subjects instead did not substantively change our results.)

Factor scores representing the shared variance of Openness, Absorption, and Psychoticism were calculated by extracting a single factor using maximum-likelihood factor analysis from BFAS Openness, MPQ Absorption, and PID-5 Psychoticism, which had loadings of .63, .98, and .72, respectively. The very high loading of Absorption on this Openness-Absorption-Psychoticism factor highlights that it does an excellent job of capturing variance that Openness shares with positive schizotypy. These factor scores were used in our subsequent analysis, although given their nearly perfect correlation with Absorption (r = .99), scores on the latter produced nearly identical results. The construction of this factor is justified by a previous analysis of this sample, which showed that, when the 10 BFAS and 25 PID-5 scales were jointly factor-analyzed together with Absorption and IQ, they showed a 10-factor structure, with one factor clearly marked by Absorption, Openness, and the Psychoticism scales. Intellect and IQ marked a separate factor (DeYoung et al., 2016; no neuroimaging data were included in this study).
Intelligence

IQ was estimated using four subtests of the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV; Wechsler, 2008): Block Design, Matrix Reasoning, Vocabulary, and Similarities. Using these four subtests is equivalent to administration of the WAIS-endorsed Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). This abbreviated assessment has excellent reliability and validity and correlates .84–.92 with WAIS-III Full-Scale IQ (Axelrod, 2002).

Image Acquisition and Preprocessing

Neuroimaging data were acquired using a 3-T Siemens Trio scanner at the University of Minnesota’s Center for Magnetic Resonance Research using a 12-channel head coil. Subjects were stabilized for head motion using padding around the head. Fast directional echoplanar imaging was acquired: time echo (TE) 86 ms; time repetition (TR) 7,900 ms; voxel size 2 x 2 x 2 mm\(^3\); 64 slices; field of view = 2048 mm\(^2\); 71 diffusion directions, and 9 measurements with b = 1,000, flip angle = 90, acquisition time 12:34. This particular sequence produces high resolution of angular information within a relatively short acquisition time. In addition, a high-resolution T1-weighted anatomical image was acquired. (MPRAGE, TR = 2,500 ms; TE = 3.34 ms; inversion time = 1,100 ms; flip angle = 7; slices = 256; voxel size = 1 x 1 x 1 mm).

The gradient direction vectors corrected for image orientation were stored in dicom files and extracted to nifti (three-dimensional diffusion-weighted image reconstruction) by the dcm2nii program (http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html). The preprocessing steps and all analyses were completed using tools included in the FMRI Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). All images were corrected for motion and eddy current distortions using the FSL tool eddy_correct. Brain extractions were completed using the FSL brain extraction tool (bet). Diffusion parameters were calculated using dftif in FSL.

Images were prepared for voxel-wise statistics using FSL’s Track-Based Spatial-Statistics (TBSS), which allows for the voxel-wise investigation of white matter diffusion parameters across the whole brain. For each subject, FA images were normalized to an FA template in Montreal Neurological Institute (MNI) space using the nonlinear registration algorithm FNIRT (FSL; http://www.fmrib.ox.ac.uk/fsl/). A mean FA image was calculated from the spatially normalized images of all subjects. This image was then “skeletonized” to allow for the comparison of FA values across spatially matched tract structures across all subjects. FA values of each subject were projected on the mean FA skeleton for use in the behavioral regression analyses.

Voxel-wise whole-brain statistical analyses were performed using the randomize command in FSL, which uses a general linear model in conjunction with 5,000 nonparametric permutation tests. Threshold-free cluster enhancement (TFCE) was used in the randomize command to calculate cluster-wise statistics corrected for multiple comparisons (Smith & Nichols, 2009). TFCE is advantageous because it avoids an arbitrarily predefined T-threshold or cluster threshold. With the obtained TFCE maps, randomize then calculates a p value for each voxel, corrected for whole brain family-wise error (FWE) rate via permutation testing. These TFCE-corrected p maps were thresholded at an FWE of .05. All reported results are obtained from these stringently corrected cluster-wise p-value maps. Anatomical results are reported using the JHU-White-Matter Tractography Atlas and the JHU ICBM-DTI-81 White Matter Labels Atlas in FSLView, and all reported coordinates are in MNI_152 coordinate space.

Per the FSL GLM recommendation, all continuous variables were mean centered before being entered into regression analyses with TBSS maps. Using FSL’s GLM tool, the central model of interest in the present study was set up to test for positive and negative linear associations between Openness-Absorption-Psychoticism factor scores and FA, controlling for Age, Sex, IQ, and BFAS Intellect. Although the main test of interest for our primary hypothesis was the negative association between the Openness-Absorption-Psychoticism factor and FA, we also tested for positive associations to determine the specificity of the effects and to test our secondary hypothesis that IQ would be associated positively with white matter coherence.

Results

Tables 1 and 2 present descriptive statistics and correlations among the behavioral measures. Our central hypothesis was supported: Significant negative associations between FA and the Openness-Absorption-Psychoticism factor scores and FA were evident across several white matter clusters in the left hemisphere (Figure 1a). These clusters were predominantly in the left frontal lobe and the left temporal lobe and include projection tracts (anterior thalamic radiation, callosal tracts (forceps minor), and association tracts (uncinate fasciculus, inferior fronto-occipital fasciculus). T-values for regions surpassing the p < .05 threshold ranged from .57 to .90. There were no white matter regions displaying significant positive linear associations between FA and the Openness-Absorption-Psychoticism factor. However, consistent with our secondary hypothesis, IQ was significantly positively associated with FA across broad regions of white matter pathways (see Figure 2).

To test whether these associations were specific to traits linked to positive as opposed to negative schizotypy, we ran a second model that included the Negative Symptom proxy as an additional predictor. No associations with Negative Symptoms were observed; moreover, the associations between FA and the Openness-Absorption-Psychoticism factor were strengthened and extended (Figure 1b), suggesting that the links between FA and psychotic-

Table 1

Sample Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full sample (N = 233; 113 females)</th>
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<tr>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Age, years</td>
<td>26.07</td>
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<tr>
<td>IQ</td>
<td>114.77</td>
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<tr>
<td>BFAS_Openness</td>
<td>3.88</td>
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<tr>
<td>BFAS_Intellect</td>
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<td>MPQ Absorption</td>
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<tr>
<td>PID-5 Psychoticism</td>
<td>1.97</td>
</tr>
<tr>
<td>Negative Symptom index</td>
<td>1.69</td>
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spectrum traits are due to the unique variance of positive symptoms.

In follow-up analyses, we examined the associations between FA and the three scales that were used to compute the Openness-Absorption-Psychoticism factor. To this end, we ran three additional randomize analyses, in which BFAS Openness, MPQ Absorption, and PID-5 Psychoticism were entered, one at a time, as predictors in place of the Openness-Absorption-Psychoticism factor, along with Intellect, IQ, and Negative Symptoms as covariates. As would be expected because of the nearly perfect collinearity between Absorption and the Openness-Absorption-Psychoticism factor, significant results obtained for the Absorption model were not appreciably different from those observed in the Openness-Absorption-Psychoticism factor model; therefore, they are not separately reported. In the models testing for inverse associations with BFAS Openness and with PID-5 Psychoticism (controlling for BFAS Intellect, IQ, Sex, and Age), no clusters were significant after FWE correction. Finally, we were interested in determining if Negative Symptoms were significantly associated with FA when the Openness-Absorption-Psychoticism factor scores were removed from the model. Results indicated that no regions approached significance (minimum cluster $p$ value = .76). (In one additional follow-up analysis suggested by an anonymous reviewer, age did not moderate the effect of the Openness-Absorption-Psychoticism factor.)

Table 2
Zero-Order Correlations Among Variables

<table>
<thead>
<tr>
<th></th>
<th>Age (M = 1, F = 0)</th>
<th>BFAS Intellect</th>
<th>BFAS Openness</th>
<th>MPQ Absorption</th>
<th>PID-5 Negative Symptom index</th>
<th>PID-5 Psychoticism</th>
<th>IQ</th>
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<td>.12</td>
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<tr>
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<td>.12</td>
<td>—</td>
<td>—</td>
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<td>BFAS Openness</td>
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<td>.06</td>
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<td>MPQ Absorption</td>
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<td>.16</td>
<td>.61</td>
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<tr>
<td>PID-5 Negative Symptom index</td>
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<td>.03</td>
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<tr>
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<td>.17</td>
<td>.64</td>
<td>.99</td>
<td>.17</td>
<td>.72</td>
</tr>
</tbody>
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Note. $N = 233$. Correlations >.12 are significant at $p < .05$.

Figure 1. Regions demonstrating significant inverse associations between FA and the Openness-Absorption-Psychoticism factor. Significant regions ($p < .05$) are displayed in red-orange, both with (1b) and without (1a) the Negative Symptom index included in the model. In Figure 1b, MNI coordinates for voxels containing the maximum $t$-value within each region are as follows: uncinate fasciculus ($t = 0.82; x = -41, y = 23, z = -9$), anterior thalamic radiation ($t = 0.48; x = -23, y = 33, z = 10$), forceps minor ($t = 0.44; x = -19, y = 36, z = 24$), inferior fronto-occipital fasciculus ($t = 0.70; x = -25, y = 32, z = 3$). (Note that because of heavily overlapping clusters, coordinates are reported only for Figure 1b.) See the online article for the color version of this figure.
To better understand the inverse association between FA and the Openness-Absorption-Psychoticism factor, we extracted the mean FA from voxels that passed the $p < .05$ threshold and examined the association of these values with our variables of interest. Although this technique will overestimate the true effect size if there are additional true associations in voxels that we were underpowered to detect as significant (Yarkoni, 2009), it is nonetheless useful for examining the relative effect sizes of the variables in question. Partial-residual plots were created in R using the functions lm and crPlots for the Openness-Absorption-Psychoticism factor as well as each of the three scales individually (see Figure 3). Each plot demonstrates associations between the variables of interest and FA after adjusting for the effects of Negative Symptoms, IQ, Intellect, Age, and Sex. The effect sizes for each of the three scales individually are closely proportional to their loadings on the Openness-Absorption-Psychoticism factor, suggesting that the lack of significant results for Openness and Psychoticism in the whole-brain analyses was probably due to a lack of power. Most importantly for our hypothesis, their shared variance shows the strongest effect and is almost perfectly approximated by the Absorption scale.

**Discussion**

Examining associations between white matter connectivity and psychosis-linked personality traits in healthy, nonpsychiatric samples is an important step in fully characterizing the continuum between health and illness in the psychotic spectrum. Our findings in a large nonclinical sample demonstrated an inverse linear association between FA and the shared variance of traits linked to psychosis-proneness in the left frontal lobe (no voxels containing positive associations were detected). This covariance was independent of sex, age, IQ, Intellect, and an index of Negative Symptoms, and it overlapped anatomically with regions putatively containing white matter endophenotypes for psychosis (Arat et al., 2015; Ellison-Wright et al., 2014; Skudlarski et al., 2013). Results from the GLM contrasts also demonstrated a positive linear association between FA and IQ, which is consistent with studies implicating white matter microstructure in the neurobiology of intelligence (Chiang et al., 2009; Navas-Sánchez et al., 2014; Penke et al., 2012; Malpas et al., 2015).

In sum, our results confirmed the hypothesized negative association of FA with an Openness-Absorption-Psychoticism factor. The identified cluster was whole-brain significant, restricted to the left frontal white matter, and almost completely overlapping with the “deep” white matter region that has been meta-analytically linked to schizophrenia and consistently identified in studies examining first-episode psychosis, high-risk samples, and first-degree relatives of psychotic-spectrum probands (Arat et al., 2015; Canu et al., 2015; Samartzis et al., 2014).

Bearing in mind that our results are merely correlational, an important question is how the observed trait-linked decreases in FA might be interpreted from a mechanistic standpoint. FA is often interpreted as an index of white matter “integrity” (health), and this may be intuitively compelling, especially in pathological samples (e.g., cases of brain injury or demyelinating illness) and given its widespread negative association with intelligence. However, integrity is not the only possible meaning of FA, and other possibilities may be particularly important when considering healthy samples. Experts have suggested that individual differences in FA in healthy samples are more likely to reflect differences in white matter organization and/or fiber count rather than differences in white matter health or integrity (Jones, Knösche, & Turner, 2013). It is difficult to say whether the schizotypy-linked connectivity patterns observed in our sample constitute the type of disconnection that is theorized to exist in patient, family-based, or high-risk samples.

We speculate that the observed FA associations in our sample may reflect individual differences in microstructural organization and/or fiber count of frontal, fronto-thalamic, temporal, and anterior callosal white matter. In this context, reduced FA may be interpreted as reflecting a more “diffuse” connectivity pattern, which may contribute to the divergent and associative cognitive style linked to Openness and positive schizotypy (DeYoung, 2015; Jung et al., 2010). It is possible that a more diffuse connectivity pattern in the frontal lobes underpins adaptive and beneficial behaviors linked to Openness (e.g., creativity, innovation, curiosity) when paired with higher intelligence and a supportive developmental environment. At the same time, when these protective factors are absent, it might predispose toward psychotic illness. In other words, the disconnection hypothesis of psychosis posits that disruptions in white matter development lead to susceptibility for psychopathology (e.g., Peters & Karlsgodt, 2015), but our results are compatible with the possibility that, although some individual differences in white matter developmental trajectories may increase risk, these individual differences may also reflect a more general association of white matter variation with individual differences in personality.
Although we did not form any specific hypotheses about hemispheric lateralization, it is worth noting that our central hypothesis was supported only in left frontal white matter. One possibility is that white matter microstructure in both hemispheres is implicated in traits linked to positive schizotypy but to differing degrees. For example, in our sample, relaxing the significance threshold from $p < 0.05$ to $p < 0.10$ for clusters in the final corrected contrast maps reveals the presence of a bilateral inverse association between FA and the Openness-Absorption-Psychoticism factor (although the left hemisphere cluster remains more extensive than the right). If this pattern is robust, then even larger samples will be required to detect it reliably at $p < 0.05$.

Despite the strengths of the present study, including large sample size, use of a community sample, detailed psychometric assessments, and high-quality neuroimaging data, limitations remain. First and most importantly, it would be premature to draw any strong etiological conclusions from our findings. In addition to the difficulty of determining the exact meaning of observed FA differences for neural health and architecture, it is also difficult to determine exactly which white matter tracts are involved (because the largest cluster we identified is traversed by several tracts). Finally, we did not conduct structured interviews or assess family history during recruitment; therefore, we do not have an optimal evaluation of the likelihood that some of our participants may go on to develop psychosis. Nevertheless, the linear nature of the associations with FA across the full range of the Openness-Absorption-Psychoticism factor (see Figure 3) suggests that the association we detected is not simply due to the inclusion of participants who will eventually experience clinical impairment.

Although we focused on structural connectivity, an important goal of future research is to combine structural and functional MRI data to better characterize the nature of the observed associations between connectivity and positive schizotypy. For example, there is evidence that thalamocortical decreases in frontal white matter FA linked to schizophrenia diagnosis mirror functional connectivity decreases between the thalamus and the dorsolateral prefrontal

Figure 3. Partial residual plots demonstrating the associations between average region of interest FA and target variables. $R$ values are partial correlations controlling for Negative Symptoms, Intellect, IQ, Sex, and Age.
cortex (Wagner et al., 2015) and that similar thalamocortical decreases are present in ultra-high-risk samples (Dauvermann et al., 2013). Determining whether or not linked structural-functional changes are systematically present across the positive psychosis spectrum is likely to aid in the interpretation of FA differences, and is an interesting and important future direction.

Identifying the specific causes and implications of trait-linked variation in FA in healthy populations is an important goal for future research. Overall, these results have important implications for basic scientific understanding of individual differences in a major dimension of personality and point to specific regions where white matter variation is likely to underpin the continuum between health and illness in the psychotic spectrum.

References


Received January 4, 2016
Revision received April 14, 2016
Accepted April 27, 2016