Personality, psychosis, and connectivity: Neuroimaging endophenotypes in the psychotic spectrum

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Dedication

This dissertation is dedicated to my mother, Holly Robinson Grazioplene (1957-2014), who loved fiercely on the edge of the abyss.

Abstract

The link between diagnoses of psychotic disorders and altered structural and functional brain connectivity is well established, yet little is known about the degree to which similar neural features 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 putative psychosis endophenotypes, this dissertation examines white matter and functional connectivity correlates of Psychoticism, Absorption, and Openness to Experience in a large community sample, covarying for sex, age, and IQ. Findings support the 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. Positive schizotypy did predict connectivity in hypothesized functional networks, but also appears positively associated with average coherence across all intrinsic networks. These findings provide biological support for the notion that liability to psychosis is distributed throughout the population, is evident in measureable neural features, and manifests as normal personality variation at subclinical levels.

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Chapter I: General Introduction & Purpose

My dissertation project will focus on examining the domain of personality traits theoretically linked to psychosis using a combination of high quality structural and functional MRI data and detailed behavioral assessments. The purpose of this project is to determine the neural correlates of trait Openness, and to test the hypothesis that the neural signatures of Openness overlap with structural and functional connectivity patterns previously associated with the positive symptoms of psychotic-spectrum disorders. This research is important for at least two major reasons: first, it aims to answer an important question for basic science ("How are individual differences in brain structure associated with individual differences in Openness, a major human personality trait dimension?"); second, it has consequences for characterizing the biological foundations of variation in personality traits that mark psychosis-proneness.

"Psychosis" is a broad term that describes a loss of contact with reality that is marked by delusions and hallucinations. Delusions involve forming fixed, false beliefs about the self, others, and reality more generally. Accumulating evidence suggests that latent risk for these symptoms is not categorical, but instead is expressed as a dimensional propensity to experience aberrant interpretations of reality, with severity on a continuum between health and illness. What are the underlying biological mechanisms that account for individual differences in psychosis-proneness? Results from large scale behavioral genetic investigations indicate that inherited liability to psychosis involves many alleles of very small effect; common variants associated with risk are normally distributed throughout the population and support a fully dimensional model of psychosis-proneness

(Grant, Munk, Kuepper, Wielpuetz, & Hennig, 2015; K S Kendler, 2014). Since these alleles, along with an unknown number of rare variants, contribute to risk via highly complex and dynamic neural system-level mechanisms, a data-driven unraveling of the etiology of psychosis appears unlikely to emerge from associating specific genes with illness—rather, it will require an overarching understanding of the features of neurobiological systems that are vulnerable to the cumulative burden of common variants, rare variants, mutation load, and environmental factors (Cicchetti & Cannon, 1999; McGrath, 2006). In other words, researchers should investigate the neural basis of relatively stable, trait-like cognitive/behavioral expressions of latent psychosis risk as it occurs along an underlying dimension (or dimensions). In order to understand such features and how they become disrupted, it is necessary to characterize the association between neural systems and traits that theoretically mark expressed risk for psychosis. The present research efforts focus on trait measures of positive schizotypy (psychosis proneness; apophenia) in both the maladaptive and the adaptive parts of the spectrum.

The dimensional latent risk model suggests that measureable (in vivo) features of neurobiological variation related to psychotic disorders are likely to be identifiable as endophenotypes that (1) reflect degree of latent genetic risk and (2) contribute to measureable trait-like 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 overinclusive thinking, whereas negative schizotypy includes physical and social anhedonia (lack of pleasure in both 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 (Kwapil et al., 2008; Goghari, Sponheim, & MacDonald, 2010). 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, neuroimaging measures, and even longitudinal prediction of psychosis conversion (e.g., Hori et al., 2013; Katagiri et al., 2015; Nettle, 2006b; 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 under-represents positive relative to negative symptoms, research on the correlates of this diagnosis will not be discussed; 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 et al., 2015; Kwapil, 2014). 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 $N = 7282$), 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, Gross, Silvia, & Barrantes-Vidal, 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 non-psychotic schizophrenia symptoms, such as anhedonia and social avoidance, but did not independently contribute to risk for psychosis when controlling for positive schizotypy (Barrantes-Vidal, Gross, Sheinbaum, & Mitjavila, 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 both clinical and nonclinical samples.

Psychosis-proneness and the Big Five

Given the evidence that dysfunctional traits, like 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 "Big Five." The Big Five personality factors constitute a reasonably comprehensive description of the most important dimensions of human individual differences in both 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, Grazioplene, & Peterson, 2012; DeYoung, 2015). 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, Quilty, & Peterson, 2007; DeYoung et al., 2012). 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; De Fruyt et al., 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; De Fruyt et al., 2012; Gore & Widiger, 2013; Markon et al., 2005, Study 2; Thomas et al., 2012; Watson et al., 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).

According to evidence from several independent samples, the difficulty in reaching consensus regarding the relation of positive schizotypy to O/I appears to stem mostly from the fact that the Openness and Intellect subfactors are differentially related to positive schizotypy (DeYoung et al., 2012). Research in both 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, in press; 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). Based on 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; DeYoung et al., in press).

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 where 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., 2015)–or to the apophenia that characterizes positive schizotypy. If this model is accurate, 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.

This dissertation utilizes multimodal neuroimaging measures to evaluate the following two-part hypothesis in a psychiatrically healthy community sample: (1) the positive symptoms of psychosis (delusions and hallucinations) can be construed as an extreme or aberrant manifestations of the Openness aspect of the O/I domain, and therefore (2) variation in brain systems linked to individual differences in questionnaire measures of apophenia and Openness will overlap with the structural and functional neural features that have been previously implicated in psychosis.

In Study 1, I will investigate associations between psychosis-linked traits (Openness, Absorption, and Psychoticism) and structural connectivity using Diffusion Weighted Imaging analyses (DWI). Diffusion-weighted MR imaging allows for the measurement of water propagation along white matter pathways, which theoretically allows for a relatively direct assessment of white matter health and connectivity patterns *in vivo*. The most commonly computed metric in diffusion weighted image analysis is *fractional anisotropy*, which is an index of the relative linearity of molecular diffusion along a principle axis in a white matter pathway. Fractional anisotropy (FA) is thought to reflect the integrity, health, and coherence of major white matter tracts in the brain (Mukherjee, Berman, Chung, Hess, & Henry, 2008). Although there is an a priori hypothesis that FA decreases will be observed in frontal, fronto-thalamic, and fronto-temporal pathways, analyses will run whole-brain regressions to ensure regional specificity.

Study 2 (resting functional connectivity) will examine whether the strength of resting functional connectivity in specific brain networks (the default mode network and the sensorimotor network) is positively associated with scores on scales of Openness, Absorption, and Psychoticism. Resting data was preprocessed using Independent Component Analyses (ICA) in FSL, a method of "blind source separation" that decomposes multidimensional connectivity data into independent neural networks. Linear associations will be examined between connectivity strength (aka coherence) and trait scores.

I.2 Neuroimaging & Dysconnectivity: Structural and functional brain signatures of psychosis and the apophenia spectrum

What are the neurobiological signatures of psychosis? Thousands of case-control neuroimaging investigations of schizophrenia, bipolar, and related disorders over the last 30 years reveal vast heterogeneity in findings across studies. Many inconsistencies are likely to be due to artificial diagnostic boundaries and underpowered analyses; even more troubling is the emerging evidence suggesting that brain regions classically construed as marking illness liability are confounded by disease chronicity, drug abuse, and medication effects (Zipursky, Reilly, & Murray, 2013). Heinrichs' (2005) review of biological findings describes a substantial overlap in biological phenotypic variation between samples of people with schizophrenia and psychologically healthy samples (Heinrichs, 2005), an observation which bolsters the continuous nature of latent risk and also points to the multideterministic nature of psychotic illness. Any one category or measure of neural structure/function is unlikely to account for large portions of the variance in psychotic symptom severity, and the extent to which any one aspect of neurobiology contributes to disease risk may critically depend on any number of other individual differences and/or contextual factors (e.g., intelligence, emotional stability, traumatic life events, immigrant status, genetic variants).

As issues surrounding medication confounds, disease duration, and the need to move away from diagnostic categories (and toward dimensional symptomology) are increasingly appreciated and addressed in study design, certain genetic and neurobiological patterns have begun to emerge consistently both across and within disorders in the psychotic spectrum. Broadly speaking, neurostructural and neurofunctional findings indicate that psychotic-spectrum diseases are fundamentally 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, in particular between distinct thalamo-cortical, fronto-striatal, and fronto-temporal regions (Anticevic et al., 2014; Canu, Agosta, & Filippi, 2014; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Structural connectivity is typically observed as aberrantly low between these regions (hypo-connectivity), although as the dysconnectivity label implies, some interconnections may be aberrantly high (hyperconnectivity), especially in the realm of functionally segregated network coherence (Anticevic et al., 2015; Lui et al., 2014; Ren et al., 2013). Such altered connectivity patterns are thought to lead to abnormal sensory and cognitive integration (Pettersson-Yeo et al., 2011).

In order to contextualize Studies 1 and 2, each chapter will focus on summarizing findings from diffusion MRI and functional MRI resting state studies of schizophrenia, bipolar, and schizoaffective disorder that are informed by a dimensional symptom perspective. Diffusion MRI (Chapter II) and resting state functional connectivity analyses (Chapter III) each allow for the examination of intrinsic connectivity patterns at the structural and functional level, respectively[1]. Particular attention will be paid to studies with implications for the degree to which putative psychosis-related neural phenotypes appear as endophenotypes in genetic high-risk samples, clinical high risk samples, and community samples.

Some notes on neuroimaging background and source selection

[1] Task-based functional neuroimaging studies are also likely to provide important insights (e.g. see Hager & Keshavan, 2015), but are not included in the present review because 1. Task-based studies utilize more heterogenous methods, and 2. Resting state studies provide a more macroscopic

There is an enormous literature of neuroimaging studies describing various neural signatures that mark psychotic spectrum illnesses[2]. Many of the findings reported in this literature have provided important insights regarding dysregulation in neural systems associated with psychosis; however, studies sampling from chronically ill patient populations may be fundamentally confounded by medication and disease duration. In other words, patient samples are typically composed of chronically ill patients who have a long history of prescription antipsychotic use, and therefore case-control neuroimaging studies that demonstrate significant neurological differences between patients and healthy controls may be detecting the consequences of either disease course or of chronic (and concurrent) medication effects—and, in the process, obscuring or failing to detect true neurological signatures linked to disease etiology.

The introduction of Chapters I and II will survey MRI studies that attempt to avoid these chronicity-related confounds via one of four research design strategies: 1. Studies that limit patient recruitment to first-episode psychotic patients who are drug-naïve; 2. Genetic high risk approaches that recruit first-degree relatives (either as "cases" themselves, or in addition to probands and healthy controls) 3. Studies examining Clinical High Risk samples (CHR), also called Ultra High Risk (UHR), prodromal samples, or At Risk Mental State (ARMS) samples (henceforth "CHR samples"; these studies recruit based on a psychosis risk-status assessment that is symptom-based and independent of family history); and 4. Studies that examine neural correlates of psychosis-proneness (apophenia) more broadly, in general population samples (e.g. using

[2] As of April 18th, 2015, a Web of Science search for "TITLE: (schizo* OR bipolar OR psychotic OR psychosis) AND TITLE: (MRI OR neurobio* OR neuroimag* OR brain OR fmri OR connectivity)" returns approximately 19,000 publications.

apophenia-related personality measures or assessments subclinical psychotic-like experiences in non-help-seeking populations). Meta-analytic findings from case-control studies of chronic schizophrenia, bipolar, and schizoaffective will be summarized briefly for context.

Finally, neuroimaging studies are often underpowered; in order to reduce the inclusion of false positive findings in the literature reviews of Chapters I and II, studies conducting whole brain analyses with fewer than 30 subjects per group will be excluded, unless they constitute part of a meta-analysis. Although studies with group sizes in the range of 30-60 still have suboptimal power to detect effect sizes of the magnitude typically observed in neuroimaging research (group sizes of approximately 60 are necessary to detect an effect of d = .50 with 80% power), this inclusion threshold represents a compromise between data quality and comprehensively reviewing the relevant literature (this trade-off is of particular relevance when considering the relatively sparse genetic high risk and Clinical High Risk literature). For DTI studies, only studies employing whole brain analyses will be included as background.

Chapter II: White matter correlates of psychosis-linked traits support continuity between personality and psychopathology (Study 1)

II.1 Introduction

White matter integrity is one of the most commonly assessed phenotypes in studies examining MRI correlates of psychotic spectrum mental illnesses. Diffusion-weighted MR imaging of water propagation along white matter pathways theoretically allows for a relatively direct assessment of white matter health and connectivity patterns in vivo. This neural phenotype is of particular interest to researchers interested in

psychosis due to the theory that psychosis etiology involves aberrant neural connectivity. The most commonly computed metric in diffusion weighted image analysis is *fractional anisotropy* (FA), which is an index of the relative linearity of molecular diffusion along a principle axis in a white matter pathway. Fractional anisotropy is theorized to reflect the integrity, health, and coherence of major white matter tracts in the brain (Mukherjee, Berman, Chung, Hess, & Henry, 2008). One notable limitation of measuring fractional anisotropy in vivo is that the tensor model of principle diffusion direction is less powerful in regions that contain large numbers of crossing fibers; this implies that, especially in regions containing many crossing fibers, lower fractional anisotropy may be partially attributable to macrostructural fiber organization in addition to reflecting microstructural differences. In general, patient cases display lower fractional anisotropy compared to controls across several conditions associated with poor cognitive outcomes, including traumatic brain injury, degenerative diseases (e.g. neuropsychiatric lupus, multiple sclerosis), and psychosis (Thomason & Thompson, 2011). In nonpsychiatric samples, fractional anisotropy is negatively associated with age, and positively associated with intelligence (Chiang et al., 2011; Navas-Sánchez et al., 2014), suggesting that fractional anisotropy is tapping properties of white matter that are fundamental to healthy cognitive function.

Comparing and contrasting diffusion imaging findings across studies can sometimes be difficult due to methodological issues inherent to defining and reporting precise anatomical locations in white matter. In general, diffusion imaging atlases comprise approximately 20 major anatomically distinct bilateral white matter fiber pathways called tracts. These tracts fall into five major categories: fiber tracts in the

brainstem, projection fibers (spino-cortical, brainstem-cortical, and thalamo-cortical), association fibers (cortex-cortex connections), limbic system (cingulum, fornix, and stria terminalis), and callosal fibers (corpus callosum and tapetum) (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). Although diffusion imaging studies typically use some combination of these tracts together with more precise anatomical atlas coordinates (e.g. MNI or Taliarach), many simply report tractwise results by hemisphere; this is problematic because many tracts span relatively long distances in the brain, especially association and projection tracts. Moreover, many of the major tracts overlap heavily with one another in certain regions. For example, the anterior limb of the internal capsule contains densely bundled fibers from the corticospinal tract and the anterior thalamic radiations, and a fan of fibers called the anterior corona radiata contains a mixture of projection (anterior thalamic radiation), association (superior longitudinal fasciculus), and callosal (genu of the corpus callosum) fibers. Examples of white matter tracts and their complex overlapping structure can be seen in Wakana et al. (2004) The loci/clusters identified by the majority of diffusion imaging analyses do not always cleanly map onto discrete white matter pathways. Identification of which tracts are implicated based on significant voxel clusters is a partly inductive process that relies on probabilistic structural atlases (e.g. the JSU White Matter Tractography Atlas), and it is common for several tracts to traverse a particular cluster or region of interest. Moreover, different atlases may call the same structure by a different name (e.g. the anterior thalamic radiation is subsumed under the larger set of projection fibers called the anterior corona radiata, and authors may choose to use either label). Due to such complications, the following summary aims to characterize the regions reported in each study in both

specific and broad anatomical terminology for easier comparison across studies

A recent mega-analytic assessment of the heritability of FA (multisite N=2248, children and adults) concluded that additive genetic factors account for greater than 50% of individual differences (Kochunov et al., 2014). The high heritability appears robust across samples—recent findings from the Human Connectome Project (60 monozygotic twin pairs, 57 dizygotic twin pairs, and 246 siblings) yielded heritability estimates of 70-90% for FA in adults aged 22-36 (Kochunov et al., 2015). Evidence from a large twin study by Chiang and colleagues indicates that the heritability of white matter integrity may vary across the lifespan, with genetic influences accounting for 30-40% of the variance in fractional anisotropy in adults (aged 19-55 years) and 70-80% in adolescents (12-18 years; Chiang et al., 2011) The moderate-to-high contribution of genetic factors to individual differences in white matter integrity, especially relatively earlier in development (e.g. when psychosis onset is more likely), raises the possibility that genetic influences contributing to psychosis vulnerability may be partially expressed in white matter characteristics—therefore, aberrant white matter connectivity is a promising endophenotype for psychosis-proneness.

II.1.1 Diffusion Imaging of Clinical Psychosis

There is ample evidence that white matter features are specifically linked to psychosis risk (as opposed to disease course or medication), suggesting that some genetic influences contributing to psychosis-proneness manifest in white matter structure. Most case-control studies indicate that clinical psychosis phenotypes involve widespread

reductions in white matter integrity; a meta analysis of 15 studies (including schizophrenia, schizoaffective, and first episode psychosis; total patient N=407) concluded that two regions overlapped across the majority of regions identified: these distinct "deep" white matter clusters are located in the frontal lobe and temporal lobe, respectively (Ellison-Wright & Bullmore, 2009). These two regions are notable due to their apparent hub-like nature: the frontal white matter cluster constitutes an area where at least five different major white matter pathways intersect and intertwine (the anterior thalamic radiation, the uncinate fasciculus, the genu of the corpus callosum, corticobulbar tracts, the inferior fronto-occipital fasciculus, and the cingulate bundle), while the temporal cluster is traversed by four major tracts (the splenium, the inferior fronto-parietal fasciculus, the fornix, and the inferior longitudinal fasciculus (Ellison-Wright & Bullmore, 2009). Notably, the frontal cluster is located at the most anterior end of the anterior limb of the internal capsule, which is a dense bundle of fibers radiating fromthalamic/basal ganglia regions forward to the frontal lobes Various tracts within the anterior limb of the internal capsule have been identified in diffusion tensor imaging of disorders involving psychosis almost without exception (Ellison-Wright & Bullmore, 2009). In the six years since Ellison-Wright & Bullmore's meta analysis, several diffusion imaging studies have confirmed the involvement of white matter pathways traversing (and/or adjacent to) these frontal and temporal clusters—not only in chronic schizophrenia, but also in first degree relatives, genetic high risk samples, and in community samples that have been assessed for psychosis-proneness (e.g. schizotypy, hearing voices). These studies will be summarized below.

A meta-analysis of diffusion tensor imaging in bipolar disorder (10 studies;

N=292 cases) also indicates two non-tract-specific clusters commonly replicated across the 10 studies surveyed: one in the right medial frontal lobe and one in a highly traversed region of the posterior inferior longitudinal fasciculus (Vederine, Wessa, Leboyer, & Houenou, 2011). The first of these regions appears to overlap almost precisely with the "deep" frontal white matter anatomical location identified in the Ellison-Wright & Bullmore (2009) schizophrenia meta-analysis, albeit in the opposite hemisphere. More recent reports also support fractional anisotropy reductions in the early stages of bipolar, demonstrating frontal white matter reductions in regions (genu of the corpus callosum, anterior portions of the anterior thalamic radiation) that are highly consistent/overlapping with findings from the 2009 meta-analysis (Benedetti et al., 2011).

Other studies that include both schizophrenia and bipolar cases together appear to reliably replicate the finding of attenuated fractional anisotropy in repeatedly identified hub-like integration regions where many tracts pass through, especially in white matter tracts partially or fully overlapping the deep frontal lobe hub, either in the right, left, or bilateral hemispheres (e.g. McIntosh et al., 2008; Sussmann et al., 2009).

II.1.2 Diffusion Imaging of early onset and drug- naïve psychosis

A 2013 analysis surveying studies that have investigated diffusion imaging within the first three years of psychosis concluded that white matter changes are evident early in the disease (Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2013). Across studies, patterns of reduced connectivity are consistently identified in frontal, fronto-temporal and fronto-limbic (striatal) connections, and the authors note particularly robust findings

across studies in the anterior portion of the superior longitudinal fasciculus, cingulum, uncinate fasciculus, and genu of the corpus callosum (Samartzis et al., 2013). Studies assessing fractional anisotropy in first-episode and/or first episode/never-medicated schizophrenia and schizoaffective also consistently demonstrate the involvement of frontal white matter, especially in the anterior thalamic radiation, the adjacent anterior limb of the internal capsule, and ROIs located in the "deep" frontal white matter (the frontal hub region identified by other studies (Canu et al., 2014). Notably, the largest of the studies included in the Canu et al. (2014) review supporting specific fractional anisotropy decreases in drug-naive first episode psychosis also reported regions of *increased* fractional anisotropy in patients in brainstem, cerebellum, interhemispheric pathways, and cortico-cortical pathways (Filippi et al., 2014). These regions did not overlap with the frontal and temporal regions that typically show inverse associations. Although purely speculative, one possibility is that hyperconnectivity in some regions paired with hypoconnectivity in others may reflect aspects of etiology that are present at disease onset, with initial hyperconnectivity in certain regions giving way to a more hypoconnected pattern as illness progresses.

II.1.3. Genetic High Risk samples

In order for reduced white matter integrity in frontal brain regions to be considered an endophenotype, it must be demonstrated that the phenotype is detectable in first degree relatives of psychotic probands at higher rate than in the general population (Gottesman & Gould, 2003). Are similar patterns of white matter integrity reductions also

evident in the first degree relatives of psychotic probands?

Skudlarski et al. (2013) investigated white matter connectivity in a sample of schizoaffective, schizophrenia and psychotic bipolar probands (N=35; N=109; N=63), their first degree relatives (N=43; N=95; N=64), and healthy controls (N=104). Of 76 white matter regions analyzed, psychotic probands demonstrated significantly lower fractional anisotropy across the majority of the brain compared to relatives and controls; there were no significant differences between the patient groups (although the bipolar probands displayed more variance in fractional anisotropy values compared to the other patient groups). Two regions (left anterior corona radiata and right superior corona radiata) differed significantly between the schizophrenia relatives and comparison subjects; only one region (the superior aspect of the left posterior corona radiata) differed between bipolar/schizoaffective relatives and controls. A combined analysis of all relatives compared to all proband and all controls revealed that relatives differed significantly from both groups in the genu of the corpus callosum, which is the portion of the corpus callosum that extends into the medial prefrontal cortex. In general, average fractional anisotropy values were lowest in the patients and highest in the healthy controls, with the relatives falling in between (Skudlarski et al., 2013). In addition to demonstrating that (at least in chronic illness) regional white matter abnormalities are largely overlapping between psychotic disorders, this study suggests that white matter abnormalities in psychosis represent one extreme of a biological continuum, notably in "deep" frontal lobe white matter (the genu of the corpus callosum and adjacent pathways).

A recent meta-analysis that examined the relatives of both schizophrenia and

bipolar concluded that relatives of schizophrenia patients display attenuated white matter integrity in frontal and temporal regions, as well as in the corpus callosum (Arat, Chouinard, Cohen, Lewandowski, & Öngür, 2015). Although the authors decided that results for bipolar across 9 studies were too diverse and underpowered to draw any strong conclusions, they noted that the most replicated regions included tracts heavily overlapping with those previously discussed in this review: anterior and temporal association fibers that include fronto-temporal, fronto-limbic/thalamic, and fronto-parietal pathways.

Since the publication of the Arat et al. (2015) meta-analysis of genetic high risk studies, two more studies have reported on FA changes in genetic high risk samples. One study that compared 50 first degree relatives to 50 controls identified no significant between-group differences in FA (Koivukangas et al., 2015). However, these analyses were not sensitive to regionally specific FA changes (FA values were averaged across 12 tracts), and data were collected on a 1.5T scanner, which generates noisier data compared to 3.0T MRI (Koivukangas et al., 2015). The second study was in a genetically informative sample, and assessed the genetic overlap between FA and schizophrenia liability. In a discordant twin design, the authors found that 8.1% of the genetic variance of a global measure of FA was shared with genetic variance for schizophrenia liability (Bohlken et al., 2015). Bohlken et al. (2015) also demonstrated that “connectivity of frontal and striatal brain regions encompassed the greatest proportion (85.7%) of genetically affected brain regions.

II.1.4 Clinical High Risk Samples

Compared to the literature on familial high risk, studies investigating structural connectivity in Clinical High Risk (CHR) samples are relatively more recent and tend to be underpowered. As yet, no meta-analysis of diffusion imaging in Clinical High Risk (CHR)/Ultra High Risk (UHR)/At Risk Mental State (ARMS)/prodromal phase has been conducted. At the time of this writing, only three studies (out of 14 total involving any psychosis high risk phenotype) met inclusion criteria for the present review[3] (whole brain studies with minimum criterion of N=30/group; average group size in included studies was N = 40).

CHR studies are important for the etiology of psychosis because they make it possible to identify and longitudinally examine individuals who are manifesting some risk symptoms of psychosis (Chung & Cannon, 2015). At baseline, CHR subjects can be compared to controls in order to determine whether neurological markers of risk are present before the onset of more severe illness. This design is promising for psychosis etiology because it may reveal neuropsychological and/or neurobiological factors that immediately precede the development of florid psychotic symptoms.

The largest of the three CHR studies included in this review compared 73 high risk participants to 69 patients and 39 controls, and found that risk status was associated with FA decreases in the deep frontal white matter of the left hemisphere (virtually

[3] ISI WebofScience search: (risk OR "ultra high risk" OR "clinical high risk" OR prodrom* OR ARMS OR "at risk mental state" OR PLE OR schizotyp* OR "psychotic like experiences") *AND* **TOPIC:** (psycho* OR schizo* OR bipolar) *AND* **TOPIC:** (diffusion OR DTI OR tractography OR DWI OR "white matter") *NOT***TOPIC:** (alz* OR stroke OR arterial OR attention OR cancer)
Refined by: WEB OF SCIENCE CATEGORIES: (PSYCHIATRY OR NEUROSCIENCES OR CLINICAL NEUROLOGY OR NEUROIMAGING OR PSYCHOLOGY)
Timespan: All years.

precisely overlapping with the frontal hub region discussed previously in section II.1.1), and that the high risk group had FA values intermediate between controls and patients (Lagopoulos et al., 2013). Lagopoulos et al. (2013) performed secondary analyses on the frontal cluster they identified, using classification-based probabilistic tractography (FSL's probtrackX) to examine the likelihood that specific white matter pathways traversed the significant cluster. They determined that the left Anterior Thalamic Radiation accounted for 94% of the white matter voxels in their identified ROI (followed by 4% left Inferior Fronto-Occipital Fasciculus and 1% left Uncinate Fasciculus). The Anterior Thalamic Radiation (ATR) contains reentrant thalomocortical loops projecting to and from the frontal cortices, and is thought to be the major pathway responsible for the processing and integration of salient executive information and subsequent behavioral modulation (Alexander, DeLong, & Strick, 1986; Coenen, Panksepp, Hurwitz, Urbach, & Mädler, 2012). Due to the preponderance of frontal and thalamic abnormalities in schizophrenia across both structural and functional neuroimaging studies, the ATR is a promising anatomical target for unraveling the pathophysiology of psychosis risk.

The second largest study (37 high risk, 37 controls), which examined FA differences using probabilistic tractography between the thalamus and 8 bilateral cortical regions (covering the whole brain), found that thalamic-orbitofrontal cortex connectivity was reduced in CHR subjects compared to controls, and that FA in this region was linearly positively associated with Global Assessment of Functioning (Cho et al., 2015). The third largest study (32 in each group) found no significant differences in FA, MD, RD, or AD in a whole brain comparison of controls and high risk subjects (Carletti et al., 2012).

CHR study designs are important, as they target a subpopulation in the "gray area" between health and illness. However, it should be noted that in the papers summarized above, CHR individuals are recruited from help-seeking populations (typically seeking help for anxiety, depression, and/or psychosis-linked problems). Compared to population-level assessment of high risk symptoms, psychotic-like experiences are fairly common in non-help-seeking populations (Nuevo et al., 2012; Preti et al., 2014; Welham et al., 2008), and therefore this sampling procedure is unlikely to capture a representative sample of individuals experiencing subclinical psychotic symptoms. Thus, although two of the three CHR studies noted herein constitute evidence for regionally specific white matter disruptions as an endophenotype, they should be interpreted with caution. As yet, no studies meeting sample size inclusion thresholds have examined whole brain FA in population-sampled high risk cohort (although see Drakesmith et al., 2015 for an FA-derived network efficiency investigation, and O'Hanlon et al., 2015 for a small case-control study of community-recruited high risk participants).

II.1.5 Psychosis-linked traits in the general population

As summarized thus far, case-control and genetic/clinical high risk-control diffusion imaging designs are popular and provide substantial support for the relevance of specific frontal/temporal white matter regions in psychosis risk. However, one of the foundations of the emerging continuum perspective of mental illness is the importance of utilizing continuous measures of symptom severity instead of (or in addition to) relying

on heterogenous diagnostic categories. Research has shown that failure to consider the multi-dimensionality of symptom clusters within clinical disorders may partially or even completely obscure meaningful associations among variables of interest (e.g., Chmielewski et al., 2014). Unfortunately, none of the diffusion imaging studies surveyed thus far examined linear associations between FA and continuous measures of positive versus negative symptoms—much less did they include any measure of cognitive functioning (e.g., intelligence). Intelligence is known to be an important moderator of brain-behavior associations (Colom et al., 2009), is a protective factor for psychotic-spectrum (Černis et al., 2015; Kenneth S. Kendler, Ohlsson, Sundquist, & Sundquist, 2015) and has well established associations with *increased* fractional anisotropy across the entire brain (Malpas et al., 2015).

Since additive genetic risk for psychosis is substantially shared across the population, subclinical traits linked to positive psychosis in nonclinical samples are an important piece of the puzzle in determining whether the white matter endophenotypes discussed are markers of genetic liability throughout the entire spectrum of psychosis-proneness. The final section regarding psychosis and diffusion imaging will summarize white matter investigations of any traits that are psychometrically linked to apophenia, including schizotypy, divergent thinking, and Big Five Openness/Intellect.

Openness/Intellect has been linked to white matter integrity in two studies: Jung and colleagues (2010) examined both personality and divergent thinking in a community sample (N=72); in addition to controlling for age and sex, intelligence was included as a covariate. Results demonstrated an inverse association between Openness to Experience

and fractional anisotropy in the right deep frontal white matter (anterior limb of the internal capsule, anterior thalamic radiation), as well as an inverse association between a composite divergent thinking measure in same regions in the contralateral (left) frontal lobe (Jung et al., 2010). As noted by the authors, these regions comprise a "surprisingly precise" overlap with the patterns of frontal white matter attenuation observed in psychotic spectrum disorders.

Contrary to the findings of Jung et al. (2010), Xu & Potenza (2012) found a positive association between Openness/Intellect and fractional anisotropy in frontal and frontal association fibers (N=56, clinically healthy adults). However, the authors failed to control for intelligence, and (as the authors themselves suggest), the positive associations between integrity and Openness/Intellect to are likely to reflect associations with intelligence (Xu & Potenza, 2012). To speculate: given that the positive associations were localized in regions similar to regions that, in theory, would be expected to show the inverse association of fractional anisotropy with apophenic aspects of openness, any true inverse association (if it existed) would have been obscured in these analyses. A third study that examined associations between FA and normal personality in a large nonclinical sample (N=265) found no association between Openness to Experience and white matter integrity; again, intelligence was not included as a covariate (Bjørnebekk et al., 2013).

Since the regressions conducted by Jung et al. included intelligence as a covariate, the inverse association between Openness to Experience and fractional anisotropy is likely to specifically reflect variance in the openness half (and not the intellect half) of

the openness/intellect domain—this supports the notion that while the aspect of the Openness/Intellect domain that is related to intelligence is likely to positively predict fractional anisotropy, the aspect that is related to positive schizotypy predicts attenuated fractional anisotropy. Although this finding has not been replicated, it is notable that the cluster identified by Jung et al. (2010) is localized in precisely the same frontal regions that are consistently identified in clinical-level patients and their relatives. Finally, it is worth noting that the results of Jung et al. (2010) were robust in a larger sample (N~180; R. Jung, personal communication, October 19, 2014).

One other research team has investigated whole-brain associations between fractional anisotropy and divergent thinking (but not personality) in a community sample. Findings in a sample of 55 young adults (mean age = 22) indicated a *positive* association between bilateral frontal fractional anisotropy and divergent thinking, even after controlling for intelligence (Takeuchi et al., 2010). However, personal communication from this research team revealed that the reported positive association disappeared with a much larger sample size (N~1000), and significant results demonstrated only negative associations between fractional anisotropy and divergent thinking (H. Takeuchi, personal communication, October 29, 2014).

Only two diffusion imaging studies involving psychometric schizotypy in nonpsychiatric samples could be identified. Due to problems of sample size and inappropriate dichotomization of a continuous variable, neither study constitutes particularly compelling evidence for the endophenotype status of white matter integrity in one direction or the other; each are summarized briefly for posterity. In a sample of 23

healthy controls, Nelson and colleagues (2011) examined linear associations between fractional anisotropy (median values across ten a priori identified white matter tracts) and scores on each dimension of the Schizotypal Personality Questionnaire (SPQ; Nelson et al., 2011). Results indicated that there was a significant inverse association between the SPQ cognitive-perceptual scores and fractional anisotropy in frontotemporal white matter tracts—no other SPQ factors (negative, disorganized) were significant. In other words, positive schizotypy—but not negative schizotypy—was associated with fractional anisotropy in the expected locations, and in the expected direction. The Nelson et al. (2011) study corroborates much of the white matter endophenotype literature, but was underpowered and must be taken with a grain of salt. A more recent study by DeRosse and colleagues in a larger nonclinical adult sample (N=138) also used the SPQ; however, not only did they arbitrarily dichotomize the SPQ variable into "high" and "low" groups (as opposed to log transforming the skewed data), they also neglected to consider the multifactorial structure of the SPQ, and instead simply summed across all three SPQ factors. Of the five a priori tracts for which they chose to extract mean values (cingulum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate), only the inferior fronto-occipital fasciculus was significantly inversely associated with schizotypy (DeRosse et al., 2014). [4]

These four studies that sought to link personality, divergent thinking, or schizotypy to white matter integrity are suggestive of a continuous underlying phenotype,

[4] Given that this study *did* have sufficient power to conduct a more standard whole brain regression of fractional anisotropy and SPQ factor scores, it seems likely that more typical regression analysis were carried out, but results were null and therefore not included in the publication.

but replication and extension is necessary for a complete understanding of the links between apophenia and white matter structure in nonclinical populations.

Based on previous findings, the hypothesis of Study 1 is that there will be an inverse association between FA in frontal lobe white matter (especially the Anterior Thalamic Radiation and Forceps Minor) and trait scores capturing the shared variance of Openness and positive schizotypy. It is also hypothesized that IQ will display *positive* associations with FA across broad and diffuse white matter regions. In addition to standard measures of Openness (Big Five Aspect Scales) and positive schizotypy (Psychoticism; PID-), the Absorption scale from the Multidimensional Personality Questionnaire (MPQ; Tellegen & Waller, 2008) is included as another measure of the shared variation between Openness and schizotypy. 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 subfactor specifically, especially when modeling the variance that Openness shares with positive schizotypy (DeYoung et al., 2012; DeYoung et al., in press).

II.2: Study 1 Materials and Methods

II.2.1 Sample Characteristics

Analyses were conducted using a sample of psychiatrically healthy, right-handed participants aged 20 to 40 (pre-exclusion $N = 306$) recruited via CraigsList in

Minneapolis-St. Paul, Minnesota. Subjects were screened during study recruitment for current use of psychotropic medications (anti-psychotics, anti-convulsants, and stimulants) as well as for history of neurologic or psychiatric disorders and for *current* heavy use or drug/alcohol problems (subjects were *not* excluded based on their history of alcohol and recreational drug use). Subjects were also excluded based on MRI contraindications (e.g., severe claustrophobia, ferromagnetic implants, pacemakers). The University of Minnesota institutional review board approved the study and participants provided written informed consent. Subjects were scheduled to complete an MRI scanning session and a behavioral session (on different days); of the 306 subjects who attended an MRI session, five were excluded for failure to attend their scheduled behavioral session.

Analyses were conducted in a sample of psychiatrically healthy, right-handed participants aged 20 to 40 (pre-exclusion $N = 264$) 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 (anti-psychotics, anti-convulsants, 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 artefacts, such as blurring or motion warping), and

three were excluded due to the presence of scanner artefacts (Soares, Marques, Alves, & Sousa, 2013).

II.2.2 Questionnaires & Assessments

Openness and Intellect were assessed using the Big Five Aspect Scales (BFAS), which measures 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 like "See beauty in things that others might not notice" and "Seldom daydream" (reversed), while the Intellect scale includes 10 items like "Am quick to understand things" and "Avoid philosophical discussions" (reversed). Intellect was used as a covariate in all regressions examining associations with Openness, due to its differential association with positive schizotypy (DeYoung et al., 2012).

The Absorption scale from the MPQ includes 34 items ($\alpha = .90$), 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, 1984). 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, Derringer, Markon, Watson, & Skodol, 2012), which measures the maladaptive traits listed in Section III of 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., 2012). Each facet is measured by 4 to 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.

Since negative and positive schizotypy are distinct but correlated dimensions of the schizotypy domain, it was important covary for negative schizotypy (in order to examine how specific our findings were to traits involved in positive schizotypy). A negative symptom composite was created using four facets from the PID-5. Based on the findings of structural analyses describing the associations between the MMPI-2-RF and the PID-5 (Anderson et al., 2015) as well as links between PID-5 facets and Schizoid PD (Anderson, Snider, Sellbom, & Hopwood, 2014), Negative Symptom scores were computed by averaging Intimacy Avoidance, Restricted Affectivity, Withdrawal, and Anhedonia.

Four subjects with high-quality MRI data were missing all PID-5 data due to a computer error. In order 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, PID5 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., in press; no neuroimaging data were included in this study).

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).

II.2.3 Image Acquisition and Preprocessing

Neuroimaging data were acquired using a 3T 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: TE 86 ms; TR 7900; voxel size 2x2x2 mm^3; 64 slices; Field of View=2048 mm^2; 71 diffusion directions, and 9 measurements with b = 1000, 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, time repetition [TR] = 2500 ms; time echo [TE] = 3.34 ms; inversion time = 1100 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 FMRIB Software Library (FSL 4.1.9; Smith et al., 2006; 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 dtifit 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 non-linear registration algorithm FNIRT (FSL; 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.

Voxelwise whole-brain statistical analyses were performed using the randomise command in FSL, which uses a general linear model in conjunction with 5000 non-parametric permutation tests. Threshold-free cluster enhancement (TFCE) was used in the randomise command to calculate cluster-wise statistics corrected for multiple comparisons (S. M. Smith & Nichols, 2009). TFCE is advantageous because it avoids an arbitrarily predefined T-threshold or cluster threshold. With the obtained TFCE maps, randomise 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 prior to 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 both 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 the primary hypothesis was the negative association between the Openness-Absorption-Psychoticism factor and FA, models 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.

II.3 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 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. Consistent with our secondary hypothesis, however, IQ was significantly positively associated with FA across broad regions of white matter pathways (Figure 2).

In order 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-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 randomise analyses, wherein 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 due to 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, and are therefore not reported separately. 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=0.76). (In one additional follow-up analysis suggested by an anonymous reviewer, age did not moderate the effect of the Openness-Absorption-Psychoticism factor.)

In order 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 (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.

II.3.2 Post-hoc analyses: Probabilistic Tractography

The JHU White Matter Atlas indicated that the ROI associated with the Openness-Absorption-Psychoticism Factor overlapped with four major white matter pathways: the Anterior Thalamic Radiation (ATR), the Forceps Minor, the Inferior Frontal-Occipital Fasciculus (IFOF), and the Uncinate Fasciculus. However, due to inter-subject variation and registration procedures in TBSS, it is difficult to say whether any one of these pathways makes up more of the ROI volume than the others. More reliable evaluation of exactly which pathways are involved has important consequences for understanding the nature of our observed associations. For example, if a single pathway

was predominant within the ROI, it would be reasonable to conclude that there are microstructural issues specific to that pathway. If, however, most subjects were found to have two or more pathways contributing to the ROI, organizational properties of this highly traversed frontal region are just as likely to explain the observed FA differences. This is an important step for the present study: in healthy subjects, it is not clear exactly whether FA differences should be attributed to organizational or pathophysiological differences.

In order to better characterize the relative volume of white matter pathways within the ROI, probabilistic tractography was performed on the diffusion data. Subjects' data was processed using the standard FSL bedpostx pipeline, which uses Bayesian approximation to model crossing fibers and estimate diffusion parameters at each voxel in subjects' native space. Seed-to-target classification was then performed with FSL's probtrackx using thresholded and binarized masks of the seed space (the significant ROI) and ATR, Forceps Minor, IFOF, and UF. Probtrackx registers these masks from standard space into each subjects' native diffusion space to generate probability distributions (based on 5000 samples). The resulting values at each voxel reflect the probability that the seed mask voxels are connected to any voxels in each of the four target masks. Finally, for each subject, these four seed-to-target probability images were thresholded to include the top 1% of classification probabilities, and the volumes of all thresholded seed-to-target images were extracted into text files using fslstats. See Figure 4 for a visual example of the ROI classification probabilities.

Probabilistic classification indicated that the ROI overlapped with all four tracts in all subjects. The volume percentages (percent of ROI voxels in the top 1% of

connection probability) were as follows: ATR made up 22% of the ROI (range 17-27%), the Forceps Minor made up 21% (range 20-23%), the IFOF made up 25% (range 20-33%) and the UF made up 12% (range 6-17%). On average, across subjects, 20% of the entire ROI did not contain probabilities past the 1% threshold, and are therefore considered to be likely to contain complex fiber organization—interestingly, the percent unclassified ROI voxels ranged somewhat widely among subjects, from 5%-31% of the ROI volume. However, neither variation in the percent of unclassified ROI nor the individual differences in percent ROI attributed to any of the target tracts explained individual differences in subjects' mean ROI FA. In short, these analyses did not provide much new information in terms of elucidating tract-specific sources of FA variation. Since classification analyses do confirm that the ROI is traversed by at least four white matter tracts in all subjects (to varying degrees), intersubject variation in microstructural organization (as opposed to white matter pathology or fiber count) remains a likely source of FA variation.

II.4 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 fractional anisotropy (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, Chouinard, Cohen, Lewandowski, & Öngür, 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 both 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., 2014; Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2013).

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. Integrity is not the only possible meaning of FA, however, 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 dysconnectivity that is theorized to exist in patient, family-based, or high risk samples.

Post-hoc analysis of the significant ROI indicated that at least four white matter pathways traversed the ROI in all subjects, but the relative volume of any one ROI-tract classification did not explain observed variation in ROI FA (minimum p-value = 0.11). This points to the true complexity of white matter pathways in this region. To speculate, observed FA associations in this sample may reflect individual differences in microstructural organization and/or fiber count of frontal, fronto-thalamic, temporal, and anterior callosal white matter. Although no one tract-specific subvolume of the ROI explained FA differences, it is possible that variation in fiber count across the ROI affected FA measurement. 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. The dysconnectivity hypothesis of psychosis posits that disruptions in white matter development lead to susceptibility for psychopathology (e.g., Peters & Karlsgodt, 2015), but the present 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 there were not specific hypotheses made regarding 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 this sample, relaxing the significance threshold from $p < .05$ to $p < .10$ for clusters in the final corrected contrast maps reveals the presence of a bilateral inverse association between FA and the Openness-Absorption-Psychoticism Factor (though 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 $p < .05$.

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 these findings. Probabilistic ROI classification reinforces the presence of at least four major white matter pathways, but it remains difficult to determine the exact meaning of observed FA differences for neural health and architecture. Finally, there was no administration of structured interviews or assess family history during recruitment, resulting in less-than-optimal evaluation of the likelihood that some 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 detected association is

not simply due to the inclusion of participants who will eventually experience clinical impairment.

Although the present study focused on structural connectivity, an important goal of future research is to combine structural and functional MRI data in order to better characterize the nature of the observed associations between connectivity and positive schizotypy. For example, there is evidence that thalamo-cortical decreases in frontal white matter FA linked to schizophrenia diagnosis mirror functional connectivity decreases between the thalamus and the dorsolateral prefrontal cortex (Wagner et al., 2015) and that similar thalamo-cortical 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.

In addition to the more subtle variations in ROI classification observed among subjects, raw probabilistic seed maps (sans any specific classification targets; Figure 4) point to substantial "variation on a theme" in terms of the organization of voxels with a high probability of being connected to the ROI. This rich variation highlights the fundamental information loss that is necessary for cross-subject FA comparison (i.e. the skeletonized maps represented in Figures 1-3). Future research efforts should focus on developing and implementing processing techniques that exploit this information, thus allowing for more nuanced quantifications of individual differences in white matter organization.

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.

Chapter III: Functional Connectivity and psychosis risk (Study 2)

III.1 Introduction

Disorders involving psychosis are linked not only to aberrant structural connectivity, but also to aberrant resting functional connectivity patterns (Meda et al., 2012; Satterthwaite & Baker, 2015). The "default mode network" is a well-established network that becomes more active when subjects are not engaged in externally-focused attention-demanding tasks (e.g. during mind wandering, self-reflective cognition, and episodic memory retrieval; Sestieri, Corbetta, Romani, & Shulman, 2011; Yeo et al., 2011). Several studies show that compared to healthy controls, people with schizophrenia (and their first-degree relatives) show hyperconnectivity within this network, suggesting that default mode connectivity is a potential marker for liability to psychosis (aka a neural endophenotype; Chai et al., 2011; Whitfield-Gabrieli et al., 2009).

Resting state functional connectivity can identify intrinsic patterns of neural connectivity that do not rely on specific tasks (Joel, Caffo, van Zijl, & Pekar, 2011). The "default mode network" (DMN; one of several established resting state networks) is a well-established functionally connected network of brain regions that was first

recognized as a network that becomes more active when subjects are *not* engaged in specific externally directed attention-demanding tasks. It has since been demonstrated that in addition to being a network involved in mind-wandering and imagination, the DMN is also active during attention demanding tasks that require internally directed or self-reflective cognition, including episodic memory retrieval tasks (Sestieri, Corbetta, Romani, & Shulman, 2011; Yeo et al., 2011). The DMN typically appears as synchronous neural activity in two primary network hubs, one of which is made up of a medial prefrontal region (the medial prefrontal cortex and the rostral anterior cingulate) and the other comprising a medial/parietal posterior region (the posterior cingulate cortex and adjacent precuneus); synchronous activations in the bilateral temporal lobes are also commonly reported. DMN connectivity is relevant as a potential endophenotype because of its association with imagination, empathy, and internally-directed thought, which are all disrupted in psychosis (Andrews-Hanna, Smallwood, & Spreng, 2014). Individual differences in default mode network connectivity may be an ideal paradigm for describing and examining intrinsic activation patterns in people at high risk for psychosis, and thus it may provide insight into the pathways that are involved not only in shared biological risk across the population, but also mechanisms that guard against the emergence of harmful psychotic symptoms (Whitfield-Gabrieli & Ford, 2012).

In addition to allowing for regionally specific hypothesis testing, resting functional connectivity allows for a whole brain network snapshot of connectivity patterns—this is in contrast to most diffusion imaging analyses, which do not provide any information about connectivity at the network level (although see Collin, Kahn, De Reus, Cahn, & Van Den Heuvel, 2014; Ryman et al., 2014). Heritability of network coherence

in the DMN appears to be roughly .40, and genetic variation underpinning coherence appears distinct from regional gray matter density in the regions that comprise the DMN (Glahn et al., 2010). Although .40 is moderate compared to the relatively high heritability coefficients observed from genetically informed studies of white matter anisotropy, it is also sensible in light of the fact that temporally rapid perturbations in DMN coherence can be caused quite easily by a number of external factors (learning tasks, fatigue, stress, and certain drugs, for example Guerra-Carrillo, Mackey, & Bunge, 2014; Heine et al., 2012). Since DMN network coherence appears to flexibly respond following task demands and other external factors—and perhaps even fundamentally support neural plasticity (Guerra-Carrillo et al., 2014)—it may be less reliably measured compared to a structural phenotype.

The overview of resting state fMRI findings relevant to the latent structure of psychosis will follow the same general structure as the discussion of diffusion imaging findings: after a general summary of case-control studies involving patients with chronic illness, studies recruiting first-degree relatives, ultra high risk samples, and general population samples will be discussed. Particular attention will be devoted to comparing default mode network connectivity findings across studies. Compared to diffusion imaging studies, resting connectivity analyses of psychosis-prone populations are relatively small and scarce in the literature, and so sample size restrictions will be relaxed in the following survey.

III.1.1 Functional Connectivity in Psychosis

Numerous case-control studies of chronically ill patients in the psychotic spectrum generally find that resting functional connectivity is globally reduced in patients

compared to controls (for a review, see Schmidt et al., 2015); however, results are inconsistent. The pattern of attenuated connectivity in patients—especially in the DMN—appears likely to be linked to antipsychotic medication, and is not necessarily a biomarker of etiology (Lui et al., 2014). Conflicting associations across studies may involve disease heterogeneity and multidimensionality of symptoms, which can be at least partially resolved by considering positive symptoms independently from negative and/or disorganized symptoms. At least one study has demonstrated that, even in chronic patients, there is a positive correlation between positive symptom severity and default mode connectivity (Whitfield-Gabrieli et al., 2009). A much larger study showed that compared to matched controls (N=100), patients with never-medicated first episode psychosis (N=100) also demonstrate increased functional connectivity in default mode regions (Ren et al., 2013).

III.1.2 Genetic High Risk samples

Whitfield-Gabrieli et al. (2009) demonstrated that the pattern of default mode hyperconnectivity observed in probands was also present in relatives; however, the sample size was very small (less than 15 in each group), even for an ROI analysis. Unfortunately, few studies have investigated resting connectivity in samples with high genetic risk for psychosis. Consistent with the findings of Whitfield-Gabrieli et al. (2009) a study utilizing a region-of-interest analysis in the default mode network found that, compared to healthy controls, individuals with high genetic risk for psychosis displayed hyperconnectivity in the default mode network (Shim et al., 2010). Yet another region-of-interest analysis of the default mode network also revealed hyperconnectivity in the default network of both schizophrenia patients (N=25) and their unaffected siblings

(N=25) compared to controls (N=25; Liu et al., 2012). Finally, similar results were reported in a larger sample that measured seed-based default network connectivity (Peeters et al., 2015). Peeters et al. (2015) compared patients with psychosis (N=73), their non-psychotic siblings (N=83), and healthy controls (N=72), and found that patients and their unaffected siblings had higher default network connectivity (precuneus-medial prefrontal cortex) compared to healthy controls (2015).

In studies using non-ROI-based methods, findings appear less consistent. In one study that used whole brain independent component analysis and compared both bipolar and schizophrenia first-degree relatives (N=70 and 52) to healthy controls (N=118), no within-network connectivity differences were observed in the DMN (Khadka et al., 2013). However, Khadka et al. did note that both probands and relatives shared a pattern of increased connectivity in the sensorimotor network during rest. Probands and relatives also shared a pattern of decreased connectivity in two networks: the fronto-occipital network and the frontal/thalamic/basal ganglia network (2013). It is interesting to consider that the frontal/thalamic/basal ganglia network is connected via the anterior limb of the internal capsule and the anterior thalamic radiation, which were among the most consistent regions demonstrating reduced structural connectivity linked to psychosis.

III.1.3 Clinical High Risk samples

Very few studies could be identified that examined resting connectivity in CHR samples. Of the three studies identified, one had a samples size that was too underpowered to be included (only 11 CHR subjects; Jacobson McEwen et al., 2014). The other two studies employed seed-based resting connectivity analyses of cortical-

thalamic (Anticevic et al., 2015) and cortical-striatal (Dandash et al., 2014) connectivity, and therefore did not yield any findings specific to the default mode network. However, since these studies were adequately powered and do indeed utilize intrinsic connectivity, they are described briefly. Focus on the thalamus and the striatum (respectively) as seed regions was motivated by theories of dysconnectivity that specifically implicate cortical-subcortical pathways in the etiology of psychosis. Anticevic et al. (2015) demonstrated increased connectivity between the thalamus and sensorimotor regions, but decreased connectivity between the thalamus and the prefrontal cortex. Moreover, this pattern was predicted by continuous indices of positive symptom scores across the entire sample (high risk subjects and controls; total N=397). Given that only thalamic connections were investigated, this finding is somewhat difficult to link with genetic high risk studies—however, prefrontal connectivity decreases and sensorimotor connectivity increases have been reported in other studies of psychosis risk in general (e.g, Khadka et al., 2013), so these findings are well situated in the broader literature.

The second study using a CHR sample investigated whether CHR status predicted altered connectivity between the subdivisions of the striatum (dorsal and ventral caudate and putamen) and any regions of the cortex (Dandash et al., 2014). Between group analyses revealed that CHR subjects had reduced connectivity between the dorsal caudate and both the dorsolateral PFC and the medial PFC, which closely aligns with the fronto-thalamic connectivity decreases identified by Anticevic et al. (2105). On the other hand, CHR subjects had increased connectivity between the ventral putamen and temporal/insular cortex (Dandash et al., 2014).

III.1.4 Community Samples

A handful of studies have investigated resting state connectivity in community samples using apophenia-related phenotypes, including Openness to Experience and divergent thinking (no studies examining psychometric schizotypy could be identified in the literature). One study in 39 healthy adults found that Openness/Intellect was associated with increased connectivity between the main midline hubs of the default network, in medial PFC and precuneus (Adelstein et al., 2011) while another found that Openness/Intellect was positively associated with connectivity in more parietal components of the default network (Sampaio, Soares, Coutinho, Sousa, & Gonçalves, 2013). A larger study (N=159) examining associations between resting connectivity and divergent thinking ability also found increased connectivity in the default network associated with performance on divergent thinking tasks (Takeuchi et al., 2012). This final study is of particular interest, since Takeuchi et al. controlled for intelligence in their analyses (2012). The validity of the association between Openness and the DMN is reinforced by the finding that there is a positive association between global efficiency of the DMN and Openness in two independent healthy samples (Beaty et al., 2015).

To summarize the studies involving resting connectivity and high risk samples, dearth of publications along with variation in fMRI methods (e.g. region of interest analyses vs. the independent component whole-brain analyses vs. seed-based connectivity) make it difficult to draw any general conclusions. The studies that examined the DMN explicitly did find a consistent pattern of hyperconnectivity in both patients and their first-degree relatives, and therefore provide tentative support for the biomarker/endophenotype status of DMN hyperconnectivity. Of major note, although

some studies did examine symptom scores separately, none of the resting functional connectivity studies in patients, relatives, or high risk groups attempted to delineate unique contributions of positive versus negative symptoms. Some studies do seem to suggest a specific role of positive symptoms, but whether this association is independent from (versus somewhat overlapping with) negative symptoms remains to be determined.

Based on the evidence from the studies summarized so far, it is hypothesized that positive schizotypy (the Openness-Absorption-Psychoticism Factor computed in Study 1) will be positively associated with functional coherence in the default mode network and in sensorimotor networks, independent of Sex, Age, IQ, and Negative Symptoms.

III.2 Methods & Materials

III.2.1 Questionnaires and Assessments

All self-report questionnaires and assessments are identical to those described in Study 1 (Chapter II.1-II.3)

III.2.2 Resting Functional MRI Sample & Neuroimaging

The imaging metrics for the resting functional connectivity sample are based on metrics that have been previously extracted using Independent Component Analyses (ICA; Abram et al., 2015). A total of 218 participants (50% male, mean age = 26) were retained after exclusions, and entered in the meta-level ICA (for details on the meta-ICA procedure see Poppe et al., 2013). Exclusions were as follows: six participants were

excluded due to attrition, nine for poor quality data, 31 for excessive movement during the scan (mean absolute displacement above 1.5 mm, or any absolute displacement (translations or rotations) above 2.75 mm), five for not completing the behavioral measures, and 11 for not completing the rest scan. Males and females did not differ significantly in terms of age, intelligence (IQ), or proportion that was non-White. Sample characteristics were virtually identical to those in the DTI sample (Table 1), and are not reported in a separate table.

Neuroimaging data were acquired using a 3T Siemens Trio scanner at the University of Minnesota's Center for Magnetic Resonance Research. Participants were stabilized to prevent excessive head motion and instructed to remain awake during the rest scan; to ensure wakeful rest, a basic fixation task was used, in which participants pushed a button each time a crosshair in the center of the screen changed from white to gray or vice versa (this switch occurred five times). This technique was used to ensure that subjects remained awake while minimizing eye movements (e.g. Fair et al., 2007; Fox et al., 2009). Only small differences have been reported for resting connectivity reliability across resting state instructions that vary with respect to eyes open/closed or with/without fixation (Patriat et al., 2013). Sequence parameters for the resting state scan are as follows: gradient-echo echo-planar imaging of 150 volumes; repetition time (TR) = 2 s; echo time (TE) = 28 ms; flip angle = 80°; voxel size = 3.5 x 3.5 x 3.5 mm. A high-resolution T1-weighted structural scan was collected for registration.

Pre-processing of converted nifti images was implemented using the FMRIB Software Library (FSL 4.1.9); steps included brain extraction, motion correction, grand

mean intensity normalization of the 4D dataset, high pass temporal filtering (at a filtering threshold of 0.1 Hz), and registration of functional images to high-resolution T1-weighted structural images (Wisner, Atluri, Lim, & Macdonald, 2013; Wisner, Patzelt, Lim, & MacDonald, 2013).

III.2.3: Independent Component Analysis of Intrinsic Connectivity Networks

Sixty intrinsic connectivity networks (ICNs) were produced using a meta-ICA pipeline (Poppe et al., 2013). The ICA was performed using the MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) function, part of the FSL toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC). The meta-ICA pipeline involves extracting ICAs from randomly ordered subgroups, the results of which are used as input for a meta-MELODIC extraction to derive the most consistent components at the overall group level (a detailed explanation of this procedure in the present sample can be found in Abram et al., 2015). The procedures outlined by Kelly et al. (2010) were used to identify non-cognitive components, which included components that were believed to reflect cardiac function, respiration, non-neural fluctuations, white matter tracts, or movement. A final set of 29 non-artefactual components were retained, and dual regression was used to derive spatial maps and timeseries for each subject (Beckmann, Mackay, Filippini, & Smith, 2009; Filippini et al., 2009; Wisner, Patzelt, et al., 2013; Zuo et al., 2010).

Network coherence, which reflects the mean connectivity score within each of the 28 components, was computed for each subject (Moodie, Wisner, & MacDonald, 2014; Poppe et al., 2013; Wisner, Atluri, et al., 2013; Wisner, Patzelt, et al., 2013). For each

subject, the mean of all voxels within each group-level component mask was calculated. Here, larger values represent more integrated function across voxels and thus, greater network coherence. Network coherence values were extracted for all networks for all subjects and will be used in the regression analyses (to be implemented using R software; R Core Team, 2015). A log transformation was applied to all component values to correct for a positively skewed distribution.

In order to ensure complete anatomical coverage of connectivity values in the default mode network, the final 29 ICNs were visually compared (using FSLView) to previous literature that establishes the precise anatomical structure of the default mode in large nonpsychiatric samples (Yeo et al., 2011). Six of the 29 relevant ICNs were completely or mostly overlapping with canonically defined DMN (Figure 5). In order to get a single index of DMN connectivity, coherence scores from the six DMN networks were entered into a principle component analysis. CFA results indicated that the first 2 components accounted for over 70% of the variance in coherence across the DMN network. The first component, which accounted for over 50% of the variance across the six ICNs, was retained as an index of DMN connectivity. To examine coherence in sensorimotor networks at rest, three of the ICNs were selected based on anatomical location (two supplementary motor cortex ICN, a premotor cortex ICN, and one ICN that overlapped with primary motor/sensory cortices) (Figure 6). Coherence values for sensorimotor activation were calculated by averaging across these three ICNs.

Linear associations were examined between resting coherence values and Openness-Absorption-Psychoticism Factor scores (the same scores were computed for

the DTI analyses; see Chapter II.2.2). Due to positive skew in the ICN components, coherence scores were log transformed before being entered into the regression models. All analyses controlled for mean subject motion, age, sex, Negative Symptoms, and IQ.

III.3 Results

Study 2 tested whether connectivity in the default mode network and/or the sensorimotor network was positively associated with a Openness-Absorption-Psychoticism Factor, covarying for Negative Symptoms, IQ, Sex, Age, and overall subject motion (mean displacement). As hypothesized, model results indicated a modest positive association between Openness-Absorption-Psychoticism factor scores and both DMN connectivity ($b = 0.17$, $p < 0.01$) and sensorimotor network connectivity ($b = 0.15$, $p < 0.05$). Full model results also revealed clear negative associations between coherence and Negative Symptoms (DMN $b = -0.20$, $p < 0.01$; sensorimotor $b = -0.22$, $p < 0.001$) as well significantly higher coherence in males compared to females (DMN $b = 0.20$, $p < 0.01$; sensorimotor $b = 0.16$, $p < 0.05$; Figures 5 and 6).

Specificity Analyses

Since it was important to establish the specificity of these results, I also examined the above models using coherence values from two occipital (visual) ICNs, since the literature does not support any particular hypotheses about genetic risk and resting state activity in the occipital lobe (Figure 7). Results of these analyses only partially supported specificity for the pattern of results observed in the DMN and sensorimotor networks. Although coherence in the more posterior occipital ICN was not significantly associated

with any of the target variables, the larger and more anterior occipital network showed evidence of a very similar pattern of results when compared to the DMN & sensorimotor network models: anterior occipital coherence was positively associated with Openness-Absorption-Psychoticism Factor ($b = 0.16$, $p < 0.05$) and negatively associated with negative symptoms ($b = -0.20$, $p < 0.01$). A broader analysis of ICN connectivity revealed even more serious problems for specificity. Average coherence across 21 non-artefactual networks (those that were not included as part of the DMN or sensorimotor regions) was computed and entered in place of the hypothesis-relevant networks. Results of this model indicated that average ICN coherence across all functionally relevant networks was positively associated with Openness-Absorption-Psychoticism ($b = 0.12$, $p = 0.05$) and negatively associated with Negative Symptoms ($b = -0.25$, $p < 0.001$; Figure 8; average ICN coherence was substantially higher than males compared to females ($b = 0.26$, $p < 0.001$).

Despite the small-to-moderate main effect of sex observed in each model, there was no significant interaction between sex and Openness-Absorption-Psychotism nor sex and Negative Symptoms for any of the networks (or network composites). However, given previous reports of sex differences in ICN coherence (e.g., Filippi et al., 2014; D. V. Smith et al., 2014), supplementary analyses were conducted within each sex separately. In all models for both sexes (DMN, sensorimotor, and ICN average), Negative Symptoms were significantly ($p < 0.05$) negatively related to coherence (b values ranged from -0.20 –0.28). Openness-Absorption-Psychoticism scores were significantly associated with DMN coherence only in females ($b = 0.25$, $p < 0.01$; males $b = 0.07$, $p =$

0.42), and with sensorimotor coherence only in males ($b = 0.19$, $p < 0.05$; females $b = 0.10$, $p = 0.94$). However, these results were not significant once average ICN coherence was entered as a covariate.

III.4 Discussion

Although results indicated support for a positive association of both DMN and sensorimotor resting state coherence with Openness-Absorption-Psychoticism scores, the observed pattern of results was not specific to the hypothesized networks of interest. Specificity analyses revealed that average ICN coherence (across all non-artifactual networks that did not constitute DMN or sensorimotor networks) was positively associated with Openness-Absorption-Psychoticism Factor scores and inversely associated with Negative Symptom scores. These associations were independent of Sex, Age, Intelligence, and mean subject motion.

Although this study did not propose any specific hypotheses regarding Negative Symptoms, the results warranted further examination of the nature of the observed inverse associations. Exploratory analyses indicated that Negative Symptoms were significantly inversely associated with 25 of the 29 individual non-artifactual ICNs. In terms of directional specificity, Openness-Absorption-Psychoticism appeared *positively* associated with coherence across all 29 ICNs, but this association was only significant in some networks. However, none of these latter significant associations would pass correction for multiple comparisons. Therefore, in this sample, it can only be concluded that Negative Symptoms are inversely associated with coherence across most resting ICNs in the brain, while no easily interpretable results emerged for the Openness-

Absorption-Psychoticism Factor. Although the hypothesized positive associations were evident in the DMN and sensorimotor networks, mean connectivity in other ICNs was also positively associated with the Openness-Absorption-Psychoticism Factor.

Despite the non-specificity of network values linked to positive and negative symptoms, the overall pattern may have implications for the interpretation of studies that observe group-level differences in genetic and clinical high risk samples compared to controls. Genetic and Clinical High Risk studies commonly report that risk group status is associated with higher resting connectivity in some regions and lower connectivity in others. The results of the present study suggest a more nuanced explanation of psychosis-risk-linked dysconnectivity, whereby *decreased* regions of connectivity are specifically linked to Negative Symptoms, but *increased* regions of connectivity are predicted by Positive Symptoms. Since positive and negative symptom indices are typically positively correlated in patients and high risk groups, future research efforts should model these traits simultaneously.

Chapter IV: General Discussion

Evidence suggests that psychosis proneness is best modeled as a continuum and can be incorporated into the five factor model of personality as a facet of Openness. Individuals with subclinical levels of apophenia (positive schizotypy) represent a key population for investigating the validity of proposed neural endophenotypes implicated in psychosis etiology. Neuroimaging investigations using diffusion weighted imaging and resting functional connectivity analyses suggest that, in general, apophenia is associated

with structural hypo-connectivity in specific white matter pathways, while resting functional connectivity studies point to hyper-connectivity (i.e. more highly correlated activity) in the default mode network and hypoconnectivity in the prefrontal cortex at rest. Several of the neuroimaging endophenotype studies reviewed used proband-relative-control designs, which serve to avoiding confounding issues such as illness chronicity and medication. However, relatively fewer studies directly employed continuous or multidimensional psychometric measures in their research designs, nor were there more than a handful of studies that sampled from the general population. Taken together with research demonstrating that genetic liability to psychosis is highly polygenic and distributed throughout the population, this dissertation suggests that neurobiological variation related to psychotic disorders is identifiable as a continuous phenotype that (1) reflects degree of latent risk (2) contributes to trait-like cognitive-behavioral manifestations—namely, high Openness. Examining these hypotheses in a nonclinical sample serves to avoid confounds inherent to working with patient samples, and is a crucial step for describing biological correlates of psychotic-spectrum traits as they manifest along the continuum between health and psychopathology.

Based on previous research that implicates white matter microstructure and resting functional connectivity as psychosis endophenotypes, it was hypothesized that variation in brain systems linked to individual differences in questionnaire measures of psychoticism, Absorption, and Openness would overlap with the structural and functional neural features that have been previously linked to psychosis liability. Specifically, it was hypothesized that the shared variance among these scales (computed Openness-Absorption-Psychoticism Factor scores) would be negatively associated with structural

coherence (Fractional Anisotropy) in bilateral fronto-thalamic and fronto-temporal regions, but positively associated with mean resting functional connectivity in the default mode network and sensorimotor networks.

The results of Study 1 were in line with hypothesized associations, indicating support for the endophenotype status of white matter microorganization in the left frontal lobe. The ROI included at least four major white matter pathways, supporting speculation that individual differences in organization are a likely source of FA differences in this region.

Results from the functional connectivity analyses in Study 2 were not technically null: significant positive associations were observed between Openness-Absorption-Psychoticism Factor scores and functional connectivity in the DMN and sensorimotor intrinsic connectivity networks (ICNs). However, this pattern of association was not specific to the ICNs of interest. Results suggested that positive schizotypy is positively associated with coherence across all ICNs in our sample, whereas negative schizotypy displayed inverse associations with coherence across the majority of ICNs. While intriguing, this pattern was not hypothesized and thus requires replication in an independent sample.

The extent to which the neural features linked to psychosis risk associate with continuous trait measures in community samples remains to be fully determined. As detailed in chapters II and III, a handful of studies support the hypothesis that white matter features and resting connectivity patterns are linked to apophenia-related measures in community samples (e.g. Jung, Grazioplene, Caprihan, Chavez, & Haier, 2010; Takeuchi et al., 2012). Examining the associations between neural measures of

connectivity and apophenia-linked personality traits in healthy nonpsychiatric samples is an important step in fully characterizing the range of both the psychometric and neurobiological continuum between health and illness in the psychotic spectrum. The merit of the present research is bolstered by the inclusion of an IQ measure, but the vast majority of studies examining traits linked to psychosis do not include a measure of IQ in their analyses. IQ may moderate the expression of positive schizotypy and is an important predictor of many aspects of neural variation. Study 1 indicates that positive schizotypy and IQ have diametrically opposite associations with FA, and developing an understanding how the relative balance of these traits plays out at the neural level is an important goal.

Results from this project have important consequences for a basic scientific understanding of individual differences in a major personality trait dimension, and may partially explain latent neural-level mechanisms that underpin the continuum between health and illness in the psychotic spectrum.

IV.2 What causes psychosis? Speculation and theoretical integration.

Exactly what kind of model might the findings of Studies 1 and 2 (along with the summarized literature) fit into? Despite vast research efforts, psychosis etiology remains elusive. Even the dopamine hypothesis of schizophrenia--which some have called "a nutmeg of consolation" for the discouraged psychopathology student (MacDonald III, 2013)—is far from constituting a satisfactory account of the neuroscience of psychosis. While many risk factors have been linked to schizophrenia, no known single factor (or set of factors) is known to cause psychosis. What kind of a disorder presents as a breakdown

of normal salience processing, occurs within a relatively distinct developmental window, and is not associated with any particular neural mechanism? The mysterious landscape of this disorder has led to many theories that attempt to account for such a heterogeneous causal structure. One useful and well-regarded model for understanding the brain's proximal phenotype as the result of ultimate etiological factors is the watershed model, whereby any number of heterogeneous upstream influences (e.g. single genes, developmental insults) can result in downstream effects on relatively stable (trait-like) aspects of neural function (Keller & Miller, 2006). A crucial implication of the watershed model is that proximal etiology is likely to be tied to system-level processes in the brain, and therefore the model underlines the importance of establishing psychosis endophenotypes (Cannon & Keller, 2006). In the watershed model of psychosis in particular, heterogeneous factors contribute to "upstream" hits to the system over the course of development (e.g. prenatal stress, childhood trauma/fever, risk genes), but the accumulation of these factors flows downstream to a common developmental event: the transition from adaptive salience and reality testing into a state of profoundly maladaptive altered salience and reality testing. In a way, the best question is not "what kind of a thing is psychosis?", but rather, "what kind of a brain is multiply susceptible to this final common dysfunction?"

I believe the answer is, "a brain that is evolutionarily perched on a razor's edge of cognitive flexibility and adaptive problem solving."

One prominent theory regarding the core of dysfunction in psychosis is that it is manifestations of a cognitive-perceptual state of "aberrant salience", such that both delusions and hallucinations involve aberrantly assigning importance (salience) to

internal representations and external cues (Howes & Kapur, 2009b; Kapur, 2003). To be clear, florid psychosis is the erroneous assignment of *meaning* to salient representations—however, a lower threshold for salience detection alone (e.g. a higher rate of cognitive-perceptual false positives; hyperactive pattern detection) may furnish a cognitive-perceptual world that increases risk for hallucinatory and/or delusional experiences in the first place.

Importantly, the developmental course of psychotic illness appears to begin primarily with the appearance and steady worsening of delusions, hallucinations and disorganization, whereas the negative symptoms emerge relatively later in the disease profile (e.g. Yung & McGorry, 1996). Some have speculated that positive symptoms of the psychotic syndrome constitute the core of expressed genetic risk—insofar as exacerbated salience detection leads to positive symptoms and increasingly disorganized cognition across the prodromal illness phase, whereas the negative symptoms may (or may not) arise as a consequence of prolonged positive/disorganized psychotic state—indeed, sometimes negative symptoms do not appear at all (Addington et al., 2015; Howes & Kapur, 2009a). As Chapman (1961) noticed, the most commonly observed "first changes" that patients retrospectively report as marking the beginning of their prodromal phase constitute abnormalities in attention, namely, the inability to filter out irrelevant stimuli from consciousness. Research in a large sample of youths identified as Clinical High Risk demonstrates that individuals deemed CHR nearly all demonstrate positive symptoms of varying severity, but conversion to psychosis is linked to the onset of increasingly disorganized cognition (Addington et al., 2015).

Something about the neural predispositions identified by the present analyses (decreased frontal lobe structural coherence and increased general functional coherence) may cause a propensity toward increased salience detection and increased apophenia. Under most circumstances, this does not cause problems: the individual may have an increased likelihood (due brain structure and concomitant function, and/or more temporally malleable aspects of neurotransmitter-driven function) to access a broader associative meaning space, but the brain is able to arrive at sensible solutions most of the time. In other words, these individuals may have a heightened capacity for cognitive and sensory integration, which is adaptively advantageous. In the fronto-thalamic/fronto-striatal (and maybe frontal-temporal) circuits, this propensity is linked to more diffuse structural connectivity (or, more accurately, some structural properties increase the nonlinear diffusion of water molecules). Individual differences in frontal structural connectivity (both coherence and organization) are apparent throughout the population, so we can assume that variation in this region is not maladaptive, per se.

Exact timing and precise mechanisms behind the timing of developmental shaping of childhood and adult circuits is not known, but a recent study showed that FA changes from childhood (~10 years of age) to adolescence (~14 years of age) occur as normative FA increases in the anterior-most portion of the Inferior-Frontal Occipital Fasciculus as well as increases in FA in the genu of the corpus callosum (the genu of the Forceps Minor; Yeatman, Dougherty, Myall, Wandell, & Feldman, 2012). These two regions of FA increase overlap with those of the IFOF and Forceps Minor identified in Study 1, reinforcing the idea that microstructural properties in the frontal ROI region (specifically) are the final regions involved in white matter development, and final

maturation of this frontal white matter results in normative increases in FA. These late-stage developmental increases occur in pathways that are thought to be under recent selection in the human lineage. Adaptive gains in complex sequential processing and rapid set shifting are thought to arise from human-specific evolutionary changes in frontal cortical-basal ganglia circuits (Finlay & Uchiyama, 2015; Lieberman, 2016), and these changes are thought to have given rise to the human complexities of language, culture, and art. Perhaps variation in the final stages of developmental patterning makes some individuals more susceptible to psychosis—but in the absence of additional genetic/developmental insults, individuals on this precarious edge have an elevated capacity to perceive connections and meaning in the course of their internal and external experiences. This, in turn, may confer some adaptive advantages in cognitive flexibility and creative problem solving.

Increased connectivity in certain brain regions also appears to be linked to psychosis, and may constitute an independent neural feature (distinct from frontal FA decreases) that modifies psychosis risk. In the sample used for Studies 1 and 2, FA in the ROI described in Study 1 was not correlated with coherence in any of the ICNs from Study 2 (lowest p-value = .33), and covarying for functional coherence (in any of the ICNs) did not change the significant inverse association between Openness-Absorption-Psychoticism and FA. Although mental illnesses are pervasively associated with altered DMN coherence and/or deficits in task-induced deactivation, the causes and consequences of individual differences in intrinsic functional network properties are not well understood (Broyd et al., 2009). Individual differences in coherence literally reflect average temporal correlations between voxel activity within a network. A recent fMRI

study that employed voxel-wise modeling shows that verbal semantics are richly mapped across the entire cortical surface (Huth, de Heer, Griffiths, Theunissen, & Gallant, 2016). In the high-adaptive range of resting coherence, it may be the case that increases in DMN coherence correspond the increased salience of a richer associative semantic space during internally generated thought. Perhaps higher average coherence in the DMN (and potentially other resting networks, according to the present Study 2 and others; Anticevic et al., 2015; Khadka et al., 2013) reflects the fact that activation of any one semantic concept node during mind wandering is more likely to activate relatively more potentially semantically relevant cortical regions if one is higher in Openness. This richer associative space may boost the ability to imagine novel and useful connections among otherwise diverse meaning structures, but this boost in signal space may come at the cost of a noisier associative meaning space. The notion of such a trade-off occurring in resting functional networks is speculative, but supports the idea that while high Openness reflects a propensity to detect meaningful patterns, it is also more likely to cause detection of meaningful patterns where none exist.

Even following these speculations, much remains unknown. If it's true that extreme variation in the structural and functional properties discussed herein potentiate type one errors in cognitive-perceptual experience, there remains no explanation for how they contribute to the catastrophic system-level transition to florid psychosis. Given the fact that infrequent mild psychotic experiences (and in some cases, severe experiences) are relatively common in non-help-seeking general population samples, it seems likely that the brain has feedback mechanisms in place for self-correcting when the mind has drifted too far afield. Perhaps the systems that are responsible for enacting such checks

and balances are susceptible to disruption themselves—but since they represent some final line of defense, there is nothing left to endogenously regulate the regulation (so to speak). Neuroinflammation may fit the bill for the kind of system that could run amok of its otherwise adaptive regulatory role. The elevation of neuroinflammatory markers (cytokines) and oxidative stress markers appear to immediately precede the onset of psychosis in at risk adolescents, and are also elevated in genetic high risk samples (Lizano et al., 2016; Perkins et al., 2014). Meta-analysis of genome-wide schizophrenia risk strongly implicates variation in immune-related inflammatory markers (Ripke et al., 2014). Theoretically, extreme variation in inflammatory response can arise from genetic variation and/or potentiation during pre/peri-natal illness (Chung & Cannon, 2015). If extreme inflammatory processes are enacted during a sensitive time in development of structural and functional connectivity (perhaps as the result of stress and/or trauma—perhaps even as the result of one's own increasingly strange perceptions), such processes may push individuals with innately more extreme connectivity patterns over the adaptive edge, cascading into system-wide disruptions in the networks that support conscious reality construction. Exactly what defines this "edge" for any one person may also critically depend on protective factors, including intelligence, emotional stability, and lack of developmental insults.

Taken together with the broader literature, the findings of this dissertation project support the endophenotype status of frontal lobe white matter and resting functional coherence. Although exact causes and consequences of these individual differences remain a mystery, the apparent traitlike nature of these endophenotypes highlights the importance of characterizing multidimensional risk and resilience in the general

population. Research aimed at such efforts is likely to provide crucial insights for a comprehensive understanding of how the adaptive functioning of neural systems becomes dysregulated in the development of psychosis.

Full Sample (N=233; 113 Females)				
	Mean	*SD*	*Range*	*α*
Age	26.07	4.93	20-40	–
IQ	114.77	16.82	75-158	–
BFAS_Openness	3.88	0.57	2.15-5.00	.82
BFAS_Intellect	4.02	0.51	2.65-5.00	.83
MPQ Absorption	3.10	0.75	1.65-5.00	.90
PID5 Psychoticism	1.97	0.61	1.00-3.81	.80
Negative Symptom Index	1.69	0.44	1.03-3.23	.81

Table 1: Sample Characteristics

	Age	Sex (M=1, F=0)	BFAS Intellect	BFAS Openness	MPQ Absorption	PID-5 Negative Symptom Index	PID-5 Psychoticism	IQ
Age	–							
Sex	.02	–						
BFAS Intellect	-.07	.12	–					
BFAS Openness	-.19	.06	.26	–				
MPQ Absorption	-.15	.18	.16	.61	–			
PID-5 Negative Symptom Index	-.04	.07	-.01	.03	.15	–		
PID-5 Psychoticism	-.15	.18	.12	.43	.69	.52	–	
IQ	-.11	-.02	.48	.15	.05	.05	.11	–
Openness-Absorption-Psychoticism Factor	-.16	.18	.17	.64	.99	.17	.72	.07

Table 2: Zero-order correlations among variables
Note: $N = 233$. Correlations greater than .12 are significant at $p < .05$.

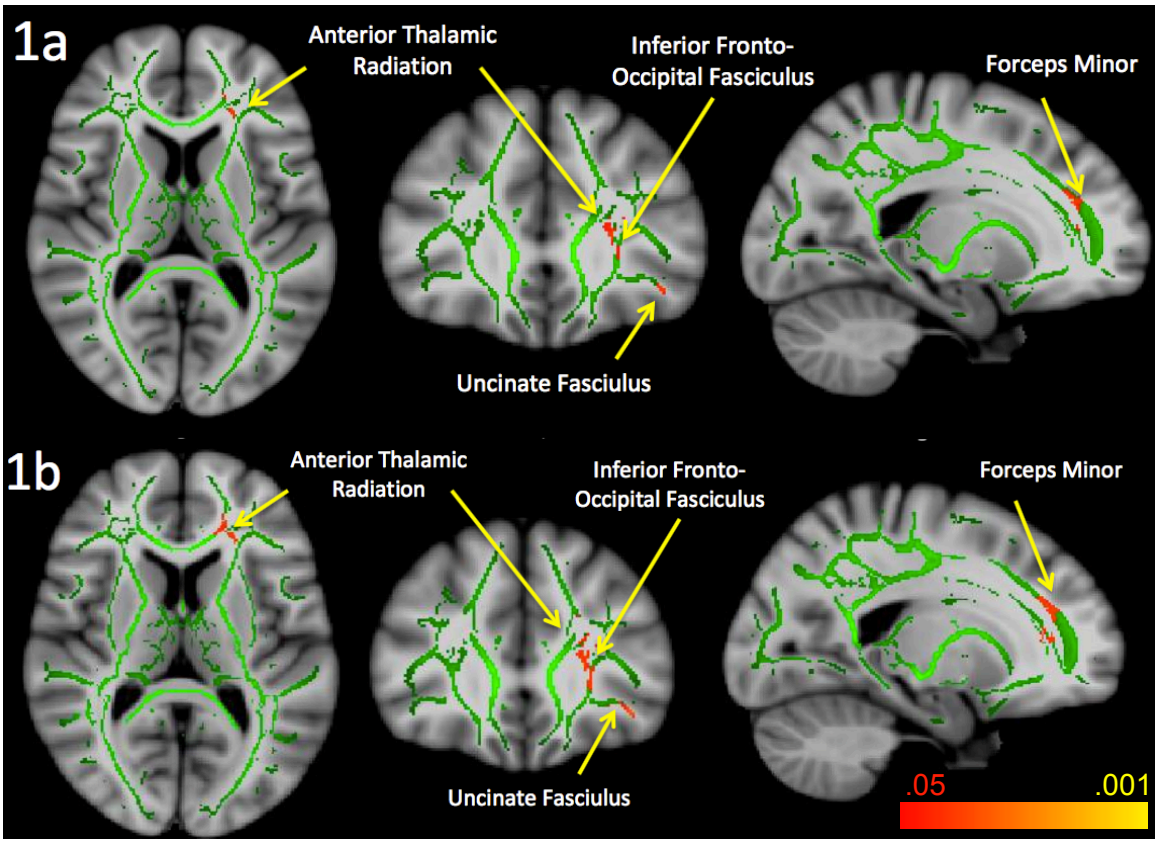

Figure 1: Regions demonstrating significant inverse associations between Fractional Anisotropy (FA) and the Openness-Absorption-Psychoticism Factor. Significant regions ($p < .05$) are displayed in red-orange, both with (1b) and without (1a) the Negative Symptom Index included in the model. In Figure 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 due to heavily overlapping clusters, coordinates are reported only for Figure 1b.)*

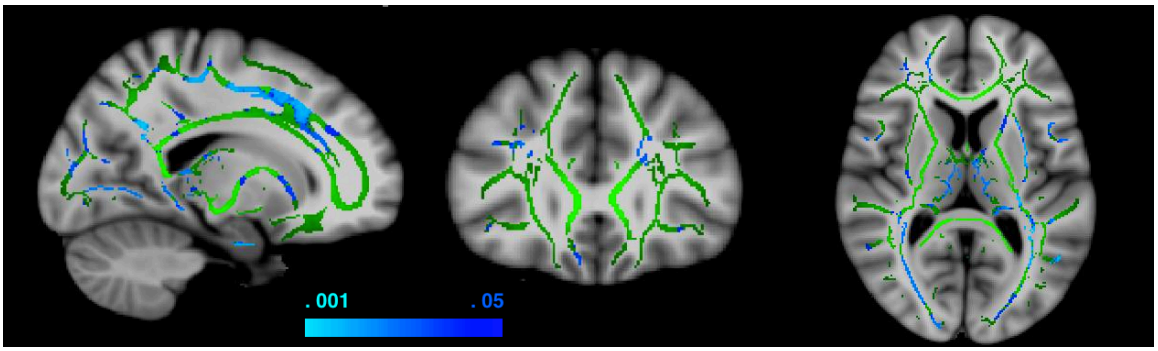

Figure 2: Significant regions demonstrating positive associations between Fractional Anisotropy (FA) and IQ. The legend denotes *p*-values corrected for both multiple comparisons and family wise error rate.

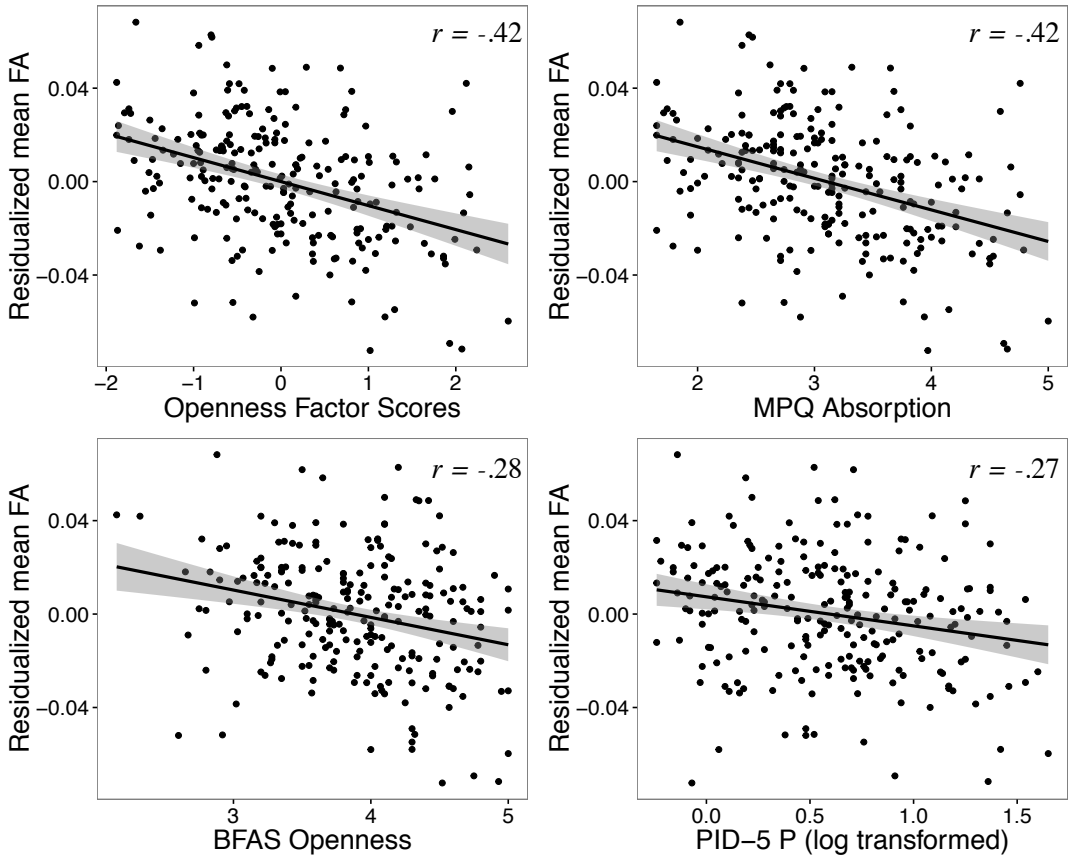

Figure 3: Partial residual plots demonstrating the associations between average ROI Fractional Anisotropy (FA) and target variables. R values are partial correlations controlling for Negative Symptoms, Intellect, IQ, Sex, and Age.

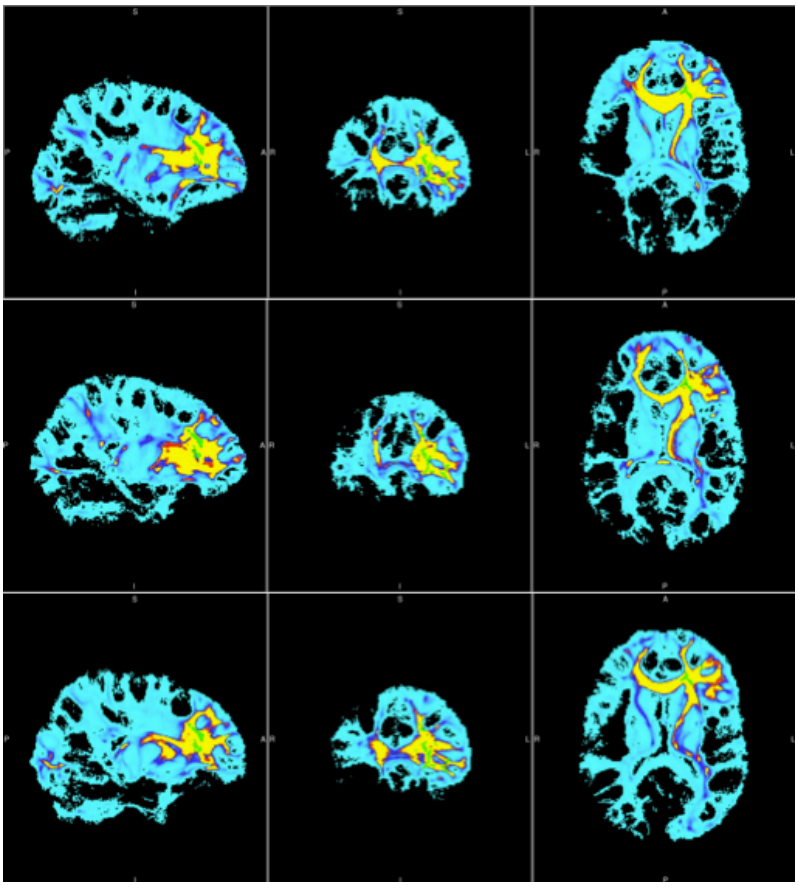

Figure 4: Examples of the pre-classification seed connectivity probabilities. Areas in yellow have the highest probability of connection with the seed ROI (green), while light blue areas have the lowest probability of connection with the seed ROI

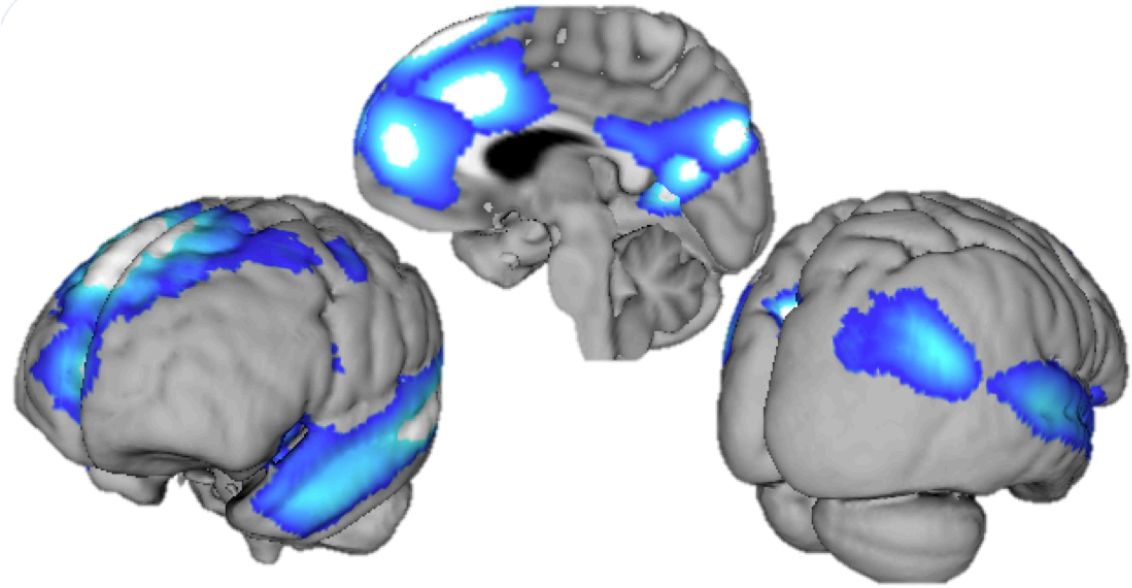

Figure 5: Default Mode Network (Anatomical maps of the six Intrinsic Connectivity Networks included in the Default Mode Network)

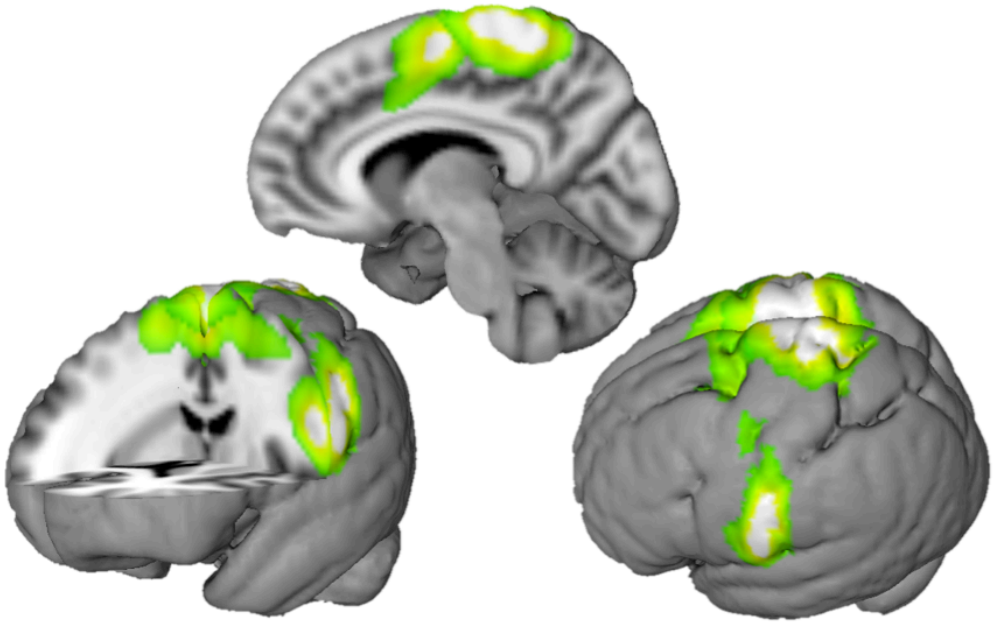

Figure 6: Sensorimotor Network: (Anatomical maps of the three Intrinsic Connectivity Networks included in the sensorimotor network)

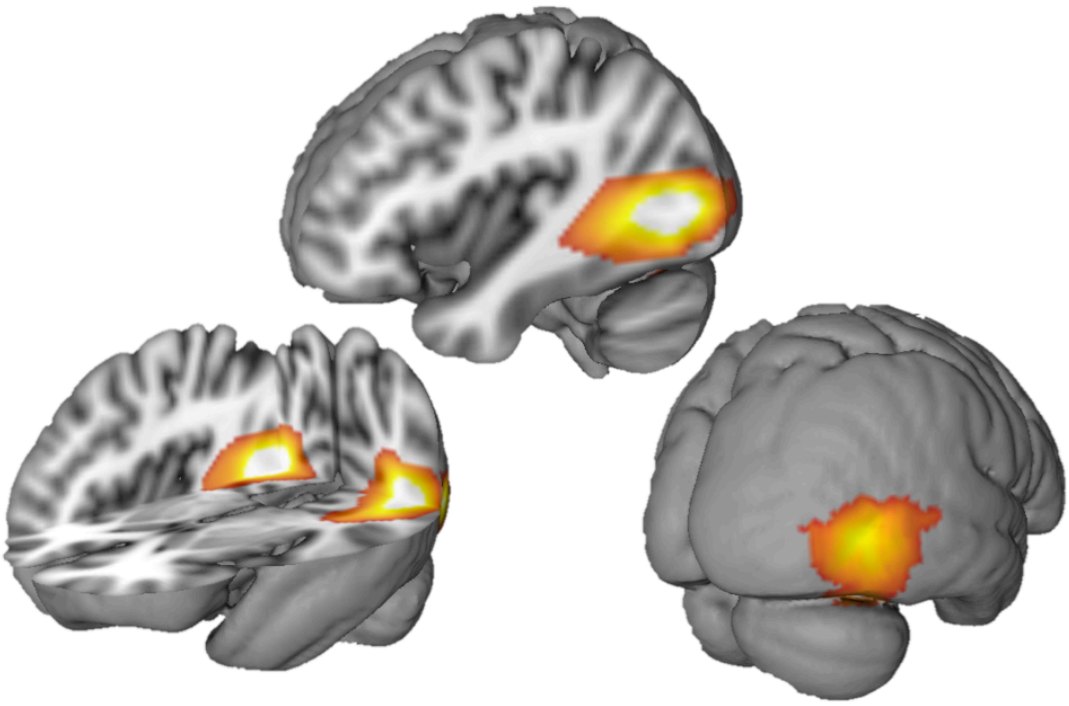

Figure 7: Medial Occipital ICN: (Anatomical maps of the single Intrinsic Connectivity Network included in the specificity analysis for Study 2)

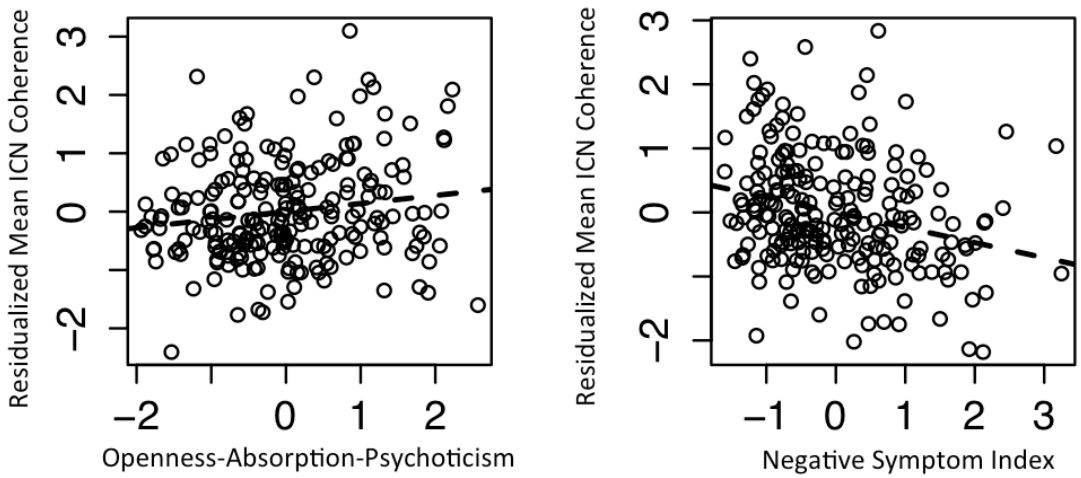

Figure 8: Partial residual plots demonstrating the associations between average ICN coherence (average across networks not involved in hypotheses) and target variables. R values are partial correlations controlling for Negative Symptoms, IQ, Sex, and Age.

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