PSYCHOSIS RISK IS ASSOCIATED WITH DECREASED WHITE MATTER INTEGRITY IN CORTICOSTRIATAL TRACTS

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The undersigned, appointed by the dean of the Graduate School, have examined the thesis entitled

PSYCHOSIS RISK IS ASSOCIATED WITH DECREASED WHITE MATTER INTEGRITY IN CORTICOSTRIATAL TRACTS

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I would like to thank my advisor, Dr. John Kerns, for his help and insight throughout this process and for his support for my research and career. I would also like to thank the other members of my committee, Drs. Bruce Bartholow, Jason Craggs, and Shawn Christ, for their thoughtful comments and feedback on this work.
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Abstract

Psychosis is associated with increased striatal dopamine and it is thought that altered connectivity between the striatum and the cortex could contribute to psychosis. In particular, there is theory and research linking psychosis to altered connectivity between the striatum and several cortical networks, especially the limbic, default mode, and frontoparietal networks. However, it is still unclear whether psychosis risk is associated with altered white matter connectivity between the striatum with any cortical region. Further, no previous study has directly examined whether psychosis risk is associated with altered connectivity with specific cortical networks. In the current study, I examined integrity of white matter tracts in psychosis risk (n=18) and non-psychosis risk comparison participants (n=19). Tracts were identified using probabilistic tractography. I found that psychosis risk was associated with significantly decreased connectivity between the striatum and the limbic cortical network, especially in the right external capsule and with connections to the right prefrontal cortex. There was a trend for psychosis risk to also be associated with decreased striatal-default mode network connectivity. However, there were no significant group differences for striatal-frontoparietal network connectivity. Hence, the current research suggests that psychosis risk is associated with decreased white matter integrity in networks involved in processing emotional and personally relevant information.
Introduction

Psychotic disorders are a severe form of psychopathology characterized by symptoms such as delusions and hallucinations, and are estimated to have a lifetime prevalence of up to 3% (Perälä et al., 2007). Psychotic disorders are often debilitating and difficult to treat. One factor that is consistently shown to improve treatment outcomes is early detection (Stafford et al., 2013). This focus on early psychosis treatment and prevention has led to a need to identify those at high risk for psychosis (e.g., McGlashan & Johannessen, 1996). Therefore, a focus of psychosis research has been identifying neurobiological antecedents of psychotic symptoms, and which of these neurobiological markers are present in psychosis risk (e.g. Pantelis et al., 2005).

Additionally, psychosis risk research removes many of the confounds present in patient research. For example, most patients with psychotic disorders are taking antipsychotic medications. Antipsychotics have widespread effects of brain structure and function, such as decreasing cortical grey matter (Scherk & Falkai, 2006), and may even lead to white matter deterioration (Szesko et al., 2014). This makes it difficult to determine if structural brain changes in patients with psychotic disorders underlie psychotic disorders or are due to the course of the disease, or confounding causes, such as antipsychotic medication.

One of the most prominent psychological theories of the development of psychotic symptoms is the aberrant salience hypothesis. Aberrant salience is experiencing irrelevant stimuli as important or self-relevant. These experiences can lead to the formation of a delusion to explain the perceived significance of these stimuli. The
putative neurobiological antecedent of aberrant salience is increased striatal dopamine (Kapur, 2003).

Increased striatal dopamine has been well-documented in psychosis (Howes & Kapur, 2009), and in psychosis risk (Egerton et al., 2013). This increased dopamine is particularly prominent in the anterior caudate (Horga et al., 2016; Kegeles et al., 2010). However, increased striatal dopamine appears to be an episodic change, only present when psychotic symptoms are present; therefore, it is often thought of as being the last step in a neurobiological cascade (Howes & Kapur, 2009; Laurelle et al., 1999). Identifying a more stable neurobiological change that is present with or without psychotic symptoms could help to develop a more comprehensive theory for the development of psychosis. Identifying changes that are present in psychosis risk, before the onset of full psychotic symptoms, could elucidate a possible trait marker for psychosis risk, which could help to identify individuals for early or preventative treatment.

The dysconnectivity hypothesis of schizophrenia proposes that aberrant connections between brain regions, both functional and structural, could lead to the development of psychosis (Pettersson-Yeo et al., 2011). Specifically, one proposed antecedent of episodically elevated striatal dopamine is disorganized white matter. White matter consists of myelinated axon tracts, which allow for fast, efficient communication between brain regions (Karoutzou, Emrich, & Dietrich, 2008). Disorganized white matter could indicate inefficiency in this communication and could underlie dysregulated activity in the affected areas (Karoutzou et al., 2008; Takahashi, et al., 2011). Disorganized white matter also fits as a neurodevelopmental theory of psychosis because myelination is not complete until early adulthood, particularly in the prefrontal cortex.
(PFC), which is also the typical age of onset for first episode psychosis (Karoutzou et al., 2008).

The theory that decreased white matter integrity could lead to dysregulated striatal dopamine and subsequent psychotic symptoms is supported by animal studies that have linked damaged white matter to increased dopamine signaling and amphetamine sensitization (Roy et al., 2007). Additionally, there is evidence of deficits in white matter in individuals diagnosed with schizophrenia. For example, several gene expression studies have indicated lower expression of genes associated with oligodendrocytes, the glial cells making up white matter in the central nervous system (Hakak et al., 2001; McCullumsmith et al., 2007). Additionally, stereological analysis has shown fewer oligodendrocytes and altered spatial arrangement of oligodendrocytes in the superior frontal lobe of individuals with schizophrenia compared to controls. This has led to a theory that white matter deficits could be a primary deficit leading to further neurobiological changes and symptoms in schizophrenia or psychosis (Takahashi et al., 2011).

Decreased white matter integrity could lead to the episodic changes in striatal dopamine seen in psychosis if it affects connections to and from the striatum. One set of pathways of particular interest are corticostriatal, which relay signals between the cortex and striatum. The striatum is the main input layer of the basal ganglia, with most areas of the cortex projecting to the striatum. Semi-parallel loops exist between cortex and basal ganglia regions, projecting from separate areas of cortex, combining in the striatum, then proceeding to other basal ganglia areas (such as pallidum and substantia nigra), to thalamus, and back to cortex (Alexander, DeLong, & Strick, 1986; Draganski et al.,
Information that is integrated and processed in the striatum and basal ganglia is sent back to cortex and plays a role in a variety of functions including limbic, motor, and cognitive processes (Averbeck et al., 2014; Di Martino et al., 2008; Haber, 2003).

It has been proposed that dysfunction of these corticostriatal connections could lead to psychotic symptoms (Robbins et al., 1990). There is evidence that in healthy individuals, cortical areas exhibit control over striatal dopamine levels (Meyer-Lindenberg et al., 2002). This theory is supported by primate studies in which dopamine could be manipulated directly. For example, Clarke and colleagues (2014) showed that depleting dopamine in the orbitofrontal cortex of monkeys lead to increased dopamine in the striatum. Additionally, human neuroimaging studies have also supported the hypothesis that disrupted corticostriatal connectivity could be related to striatal dopamine functioning (Fusar-Poli et al., 2010; Fusar-Poli et al., 2011). This evidence suggests that decreased white matter integrity in psychosis risk could disrupt communication between cortical regions and striatum, leading to striatal dopamine dysregulation, and subsequent psychotic symptoms. However, to my knowledge, white matter integrity of corticostriatal connections has never been examined in psychosis risk.

Diffusion tensor imaging (DTI) allows for in-vivo examination of white matter by measuring the diffusion of water molecules. One measure of white matter integrity, fractional anisotropy (FA) measures the restriction of the diffusion of water molecules throughout different types of brain tissue. FA ranges from 0 (isotropic) to 1 (anisotropic) with 0 representing equal diffusion in all directions, such as in liquid, and 1 representing diffusion that is restricted completely to one direction, such as a well-organized white matter tract with all axons running in parallel. FA is sensitive to a variety of white matter
changes, and is the most widely used measure of white matter integrity (Alexander et al., 2007).

DTI analyses of patients with psychosis, even first episode psychosis (FEP), often have found decreased white matter integrity (Alvarado-Alanis et al., 2015; Kawashima et al., 2009; Lee et al., 2013; Luck et al., 2011; Moriya et al., 2010; Pérez-Iglesias et al., 2010). However, findings in psychosis risk subjects have been mixed, with some studies finding decreased white matter integrity in certain brain regions, and others finding no differences (see table 1). Table 1 shows the findings of studies examining white matter integrity, as assessed by FA, in psychosis risk, both at the whole-brain and region of interest (ROI) level of analysis. Most importantly, to my knowledge, no previous study has examined white matter integrity in corticostriatal tracts, despite the theoretical significance of corticostriatal connections to the development of psychotic symptoms.

Because different striatal subregions have distinct connections with different cortical regions (Alexander et al., 1986; Haber & Knutson, 2010), we investigated connections between striatal subregions and different cortical networks. In order to identify white matter tracts connecting cortex to specific striatal subregions, we examined regions identified by Choi, Yeo, and Buckner (2012). Choi and colleagues utilized resting state fMRI to examine functional connectivity between the striatum and seven different cortical networks: default mode, dorsal attention, frontoparietal, limbic, motor, ventral attention, and visual. Connectivity was first examined in a large sample of 500 subjects, then replicated in a second, independent sample of 500 subjects. Each striatal voxel was assigned to the cortical network to which it was most strongly connected. Of particular
interest are the networks comprising the limbic and associative striatum, as these striatal subregions, especially anterior caudate, have been implicated in the development of psychosis (Howes et al., 2007). Specifically, the limbic striatum (primarily ventral anterior caudate; nucleus accumbens) was found to be connected to the limbic cortical network. The associative striatum (primarily dorsal anterior caudate and the posterior caudate) was found to be connected to both the default mode and frontoparietal cortical networks.

One prominent model of the pathophysiology of schizophrenia conceptualizes the disorder as arising from dysfunction related to the limbic striatum (Grace, 2000). Limbic striatum receives dopaminergic innervation from limbic structures, such as the ventral hippocampus and the amygdala, as well as cortex, particularly medial PFC. The limbic striatum then integrates these inputs and projects to other basal ganglia structures, which in turn project to cortex and thalamus and help to shape motor and goal-directed behavior (Goto & Grace, 2008). It has been proposed that hippocampal dysfunction leads to dysregulation in the limbic striatum and PFC and a hyper-responsive dopamine state in the limbic striatum which all stimuli, regardless of importance, are capable of producing a maximal dopamine signal, leading to the experience of aberrant salience (Grace, 2016). Human neuroimaging studies have also supported this hypothesis. Specifically, Roiser and colleagues (2012) found that activation in the limbic striatum to irrelevant stimuli was increased in individuals at clinical high risk for psychosis and was associated with aberrant salience. Therefore, the limbic striatum and its connections are hypothesized as being critical in the development of aberrant salience, and possibly in subsequent psychotic symptoms.
The associative striatum has also been implicated in the development of psychosis, particularly the anterior caudate (Horga et al., 2016; Kegeles et al., 2010). Both the default mode and, to a lesser extent, the frontoparietal cortical networks were found to be connected to the associative striatum (Choi et al., 2012). Specifically, the default mode comprises most of the anterior caudate and hence may be more relevant to psychosis. The frontoparietal subregion overlaps with the anterior caudate, but also extends into the posterior caudate, and may be less relevant than the default mode subregion (Choi et al., 2012).

The default mode cortical network includes the cortical regions that are more active at rest than during tasks. Default mode network is involved in processing self-relevant cognitions (Qin & Northoff, 2011). Disruption of the default mode network could be related to dysregulated self-relevance signals as seen in aberrant salience. Individuals with high familial risk for psychosis have shown decreased functional connectivity in the default mode network (Jukuri et al., 2013).

The frontoparietal network includes regions throughout the frontal and parietal lobes, including lateral PFC, dorsomedial PFC, and parietal association cortex. These regions are often active during attentional processes and inhibition (Dodds et al., 2011). Frontoparietal network has been conceptualized as a control system of the brain, initiating and adjusting control and inhibition of subcortical regions (Dosenbach et al., 2008). Disruption of the frontoparietal network could lead to an inability to self-regulate and inhibit aberrant signals when they emerge. To my knowledge, no past studies have examined functional connectivity in the frontoparietal network for psychosis risk, but this
network has shown decreased frontoparietal connectivity in schizophrenia (Baker, et al., 2014).

The current study will examine white matter integrity (measured with FA) in the connections between striatal subregions and the limbic, default mode, and frontoparietal cortical networks. To my knowledge, no previous study has examined white matter integrity in psychosis risk in corticostriatal tracts despite their possible relevance to the development of psychosis. I hypothesize that I will find decreased white matter integrity, as evidenced by decreased FA, within these tracts, especially within the limbic network and default mode network, networks most related to the anterior caudate and most often implicated in psychosis risk (Grace, 2000; Horga et al., 2016).
Method

Participants

Participants (n=37) were recruited from introductory psychology courses at the University of Missouri and received course credit for their participation. All participants spoke English as a first language and were right-handed. Participants were recruited through a multi-step process to identify psychosis risk based on both self-report and interview-rated psychotic-like symptoms, which has been used in previous research (Cicero et al., 2014; Karcher, Martin, & Kerns, 2015). First, all participants completed the perceptual aberrations (PerAb; Chapman, Chapman, & Raulin, 1978) and magical ideation (MagicId; Eckblad & Chapman, 1983) Wisconsin schizotypy scales. PerAb and MagicId are both indicative of positive psychotic-like symptoms and are highly correlated. Therefore, we used previously established criteria to combine these scales in order to create one PerMag group of participants who were elevated on either or both scales (Chapman et al., 1994). Participants who scored 1.96 sex-normed standard deviations about the mean on either PerAb or MagicID or who scored a combined 3 sex-normed standard deviations above the mean on both PerAb and MagicId were considered to have extreme positive schizotypy. Importantly, self-reported schizotypy alone is not a good predictor of development of psychosis (Chapman et al., 1994). Therefore, all Per-Mag participants were interviewed to assess attenuated psychotic symptoms.

Next, a senior graduate student administered the Structured Interview for Psychosis Risk Syndrome to all participants (SIPS; Miller et al., 2003). Participants who endorsed both moderate attenuated psychotic symptoms (a score of 3 or above on the SIPS) and extreme positive schizotypy, were considered at high risk for psychosis.
Previous research has found that individuals with both extreme positive schizotypy and attenuated psychotic symptoms are at increased risk of developing a psychotic disorder (Chapman et al., 1994). Specifically, this psychosis risk group is estimated to have a 22% lifetime prevalence of psychotic disorders (based on Pedersen et al., 2014), which is similar to the prevalence rate seen among first-degree relatives of those with a psychotic disorder (Fardi et al., 2009). Participants in the psychosis risk group (n=18) had a mean age of 18.33 years (SD=0.594) and were 66.7% female, 66.7% Caucasian, 27.8% African-American, and 5.6% Asian-American.

The control group consisted of participants who did not endorse attenuated psychotic symptoms (i.e. SIPS score < 3), and who scored between -0.6 and +0.6 sex-normed standard deviations from the mean on the PerAb and MagicId scales. Thus, the control group was near the population mean on positive schizotypy, and not extremely low on positive schizotypy. Additionally, all participants in the control group scored between -0.5 and +0.5 sex-normed standard deviations from the mean on the Revised Social Anhedonia Scale (SocAnh; Eckblad et al., 1982), showing that the control group was near the population mean on negative schizotypy, as well as positive schizotypy. This is important as SocAnh has been found to predict non-psychotic Schizophrenia-Spectrum disorders (Debanné et al., 2015). Participants in the control group (n=19) had a mean age of 18.37 years (SD=0.597) and were 73.7% female, 89.5% Caucasian, 5.3% Asian-American, and 5.3% biracial. There were no significant differences between the psychosis risk group and the control group on sex ($\chi^2 [1, N = 37] = .218, p = .728$), ethnicity($\chi^2 [3, N = 37] = 6.84, p = .077$), or age ($\chi^2 [2, N = 37] = .084, p = .959$).

**Materials**
Wisconsin schizotypy scales. Schizotypy refers to a continuum of psychotic-like traits, less severe than seen in a fully psychotic state (Meehl, 1962; Raine 2006). In the current study, schizotypy was assessed with the perceptual aberrations (PerAb; Chapman, Chapman, & Raulin, 1978), magical ideation (MagicId; Eckblad & Chapman, 1983), and social anhedonia (SocAnh; Eckblad et al., 1982) Wisconsin schizotypy scales. PerAb is a 35-item true/false scale, which assesses distortions in the perceptions of one’s own body. MagicId is a 30-item true/false scale, which assesses the endorsement of abnormal and magical beliefs. SocAnh is a 40-item true/false scale, which assesses a lack of pleasure from non-physical stimuli, such as social relationships. Consistent with previous research, scores on each of these scales were standardized within sex (e.g., Eckblad & Chapman, 1986; Kerns, 2006).

Structured interview for psychosis risk syndromes. The structured interview for psychosis risk syndromes (SIPS; Miller et al., 2003) is a semi-structured diagnostic interview assessing attenuated psychotic symptoms, and has been shown to predict future development of a psychotic disorder (Miller et al., 2003). In line with previous research, participants who were rated as having moderate psychotic-like symptoms (score of 3 or above) on either the Perceptual Abnormalities/Hallucinations or Unusual Thought Content/Delusional Ideation domains of the SIPS were classified as at risk for psychosis (e.g., Karcher, Martin, & Kerns, 2015). All interviews were conducted by an advanced graduate student, blind to group membership, and were videotaped.

Image acquisition

Diffusion-weighted data were acquired on a 3T Siemens MRI scanner using a standard 8-channel head coil. Two runs of singleshot spin-echo echo-planar DTI (SE-
EPI-DTI) with TR=9900 ms, TE=102 ms, FOV=190 mm x 190 mm for 60 contiguous axial slices without gap, a slice thickness of 2 mm, and a matrix size of 96 x 96. 25 noncollinear diffusion gradient directions were acquired with b=1000 s/mm weighting, and one b=0 s/mm image was also acquired.

**Image Preprocessing**

Data preprocessing was carried out using the functional MRI software library (FSL; Smith et al., 2004). Images were corrected for the effects of eddy currents and head movements. Then, a brain mask was created for each participant based on the first of the B=0 (no diffusion weighting) images from the start of the scan by extracting the brain matter from non-brain matter using the brain extraction tool (BET; Smith et al., 2002). Finally, the FSL-DTIFit program was used to locally fit diffusion tensors to the images, and derive fractional anisotropy (FA) measurements.

**Tract-based Spatial Statistics**

FSL’s tract-based spatial statistics (TBSS) was used to perform voxelwise statistical analysis for each subject’s FA measurement (Smith et al., 2006). All subjects’ FA were aligned onto a common space, created from a template derived from comparing all subjects using FSL’s nonlinear registration tool (FNIRT; Andersson et al., 2007). Then, mean FA skeletons were created, which show the white matter tracts common to all participants. A threshold of 0.2 FA was used to ensure that only white matter was included in the skeletons, and that voxels where the program was unable to attain a good alignment were excluded.

**Region of Interest Analysis**
To investigate corticostriatal connections, I used the regions of interest (ROIs) identified by Choi and colleagues (2012). Choi and colleagues examined functional connectivity between seven cortical networks and the striatum, identifying the striatal regions most strongly connected with each cortical network. Of particular interest, are the limbic, default mode, and frontoparietal cortical networks (see figure 1).

Bayesian estimation of diffusion parameters obtained using sampling techniques (Bedpostx; Behrens et al., 2007) was run on each subject’s brain mask to calculate diffusion parameters and count the number of crossing fibers in each voxel. This creates the necessary inputs to run probabilistic tractography.

Probabilistic tractography was used to identify corticostriatal tracts (Behrens, 2007). The striatal ROIs identified by Choi and colleagues for striatal limbic region, striatal default mode region, and striatal frontoparietal regions were used as seed regions, and the corresponding cortical regions—limbic cortical network, default mode cortical network, and frontoparietal cortical network—were used as waypoint masks. Nonlinear transformations were used to transform ROIs from MNI 1mm standard space into each subject’s diffusion space, where probabilistic tractography was performed, then the inverse transformation was used to transform the results from probabilistic tractography back into MNI 1mm standard space for further analysis (Andersson et al., 2007). A connectivity distribution was built for each striatal seed region by creating 5000 sample paths from each voxel in the seed region, and using modified Euler streaming to identify possible tracts. Paths that crossed the waypoint mask (e.g., from striatal default mode region to default mode cortical network) were kept. Paths that did not cross the waypoint mask were discarded. In order to exclude implausible pathways, paths were terminated if
they would involve a turn or +/-80 degrees, they looped back onto themselves, or they reached 2000 steps of .5mm (meaning paths were 1m in length).

Each voxel was given a number of how many paths passed through that voxel, which represents the connectivity value of that voxel with the striatal seed and cortical mask. This resulted in a single image for each connection (i.e., limbic, default mode, and frontoparietal) for each subject, containing a value in every voxel. As is standard with probabilistic tractography (Morris et al., 2008), I used a threshold to eliminate from tracts any voxels with a low connection probability. Most recent studies have thresholded each participant’s data by a percentage of the maximum connection strength within their own data, which assures that all participants’ contribute to the final ROI (Bennett et al., 2011). Common thresholds used have been between 10% (Robinson et al., 2012; Teichmann et al., 2015) to 25% (Khalsa et al., 2014; Kinoshita et al., 2015). I chose 10% as the threshold in the current study because I also used modified Euler streaming, which not only results in more accurate tracts, but also then typically yields lower connectivity values than in studies that used a higher threshold. Hence, with modified Euler streaming that seemed to make a lower threshold more sensible, whereas a higher threshold would be more likely to erroneously remove valid voxels from tracts.

Next, each subject’s thresholded image was binarized, and these binarized images were summed together. Then, this summed image was thresholded to discard voxels that were present in the tract for less than one fourth of the participants (n=9). Then, this image was masked with the mean FA skeleton mask (created by TBSS) to identify regions within the core of white matter tracts and to make sure that all voxels in the ROI were truly white matter. Finally, this image was binarized to create an ROI, resulting in
one ROI for tracts connecting striatal limbic region to limbic cortical network, from here on referred to as limbic white matter (WM) ROI, one ROI for tracts connecting striatal default mode region to default mode cortical network, from here on referred to as default mode WM ROI, and one ROI for tracts connecting the frontoparietal striatal region to frontoparietal cortical network, from here on referred to as the frontoparietal WM ROI (see figure 2).

The ROIs were used to mask each subject’s FA images to create an image containing each subject’s FA values for each voxel in the ROI. These images were analyzed in several ways. First, mean FA for the whole brain was calculated for each participant by averaging across all voxels in the skeleton using fslstats (Jenkinson et al., 2012). A t-test was performed in R to see if there were differences between psychosis risk and controls in mean FA in the whole brain.

**Permutation Analyses**

For ROIs in which a t-test revealed a significant difference in FA between psychosis risk and controls, these results were followed up in two ways, with a permutation test and by further dividing the ROI into component regions. The randomise tool in FSL was used to carry out the permutation analyses. The randomise tool creates permutations of the data to compare two groups and to test for the likelihood of a significant different cluster of white matter voxels between groups within the broader ROI without making any assumptions about the null distribution from which the data arises (Winkler et al., 2014). For this analysis, all subjects’ FA images were combined to create a 4D data file holding values for each subject. Then, the randomise procedure was used to create 500 permutations to compare psychosis risk and controls on FA. This
analysis calculates the probability that each voxel significantly differs between groups, then uses threshold-free cluster enhancement (TFCE) to keep the overall corrected error level at \( p<.05 \) while correcting for multiple comparisons and to identify specific clusters where FA significantly differs between groups.

**Component Regions Analysis**

As an additional follow-up for ROIs that showed significantly different FA between psychosis risk and controls, each ROI was further broken down into subregion component ROIs by hemisphere and lobe. In order to investigate whether decreased FA was equally spread across WM ROI tracts or if specific components of the networks were more affected than others, I investigated tracts connecting the specified striatal region to components of the specified cortical network, broken up by hemisphere and lobe. For instance, the overall limbic cortical network is comprised of bilateral regions in the frontal and temporal lobes. Hence, I broke up the limbic cortical network into four regions: right frontal region, left frontal region, right temporal region, and left temporal region and examined tracts connecting the limbic striatum with each of these four subregions separately.

WM ROIs connecting the striatal subregion to each of these component cortical networks was determined in the same manner described above to find the original set of WM ROIs. Then, these component WM ROIs were analyzed using a t-test to determine if FA in this ROI significantly differed between psychosis risk and controls.

**Whole Brain Analysis**

In addition to analyzing the regions of interest described above, I also analyzed FA across the whole brain. First, I used a t-test to examine whether there were differences
in FA between the groups for across all white matter tracts. Next, I used whole brain analyses to examine whether there were any between-group differences in any white matter clusters outside of striatal tracts.
Results

Limbic Network

I first compared the groups in mean FA in the limbic network white matter ROI. In this ROI, there was a significant difference between the two groups, \( t(35)=2.310, p=0.026 \). In particular, the psychosis risk group had significantly decreased FA in limbic network white matter tracts.

I followed up this significant result in two ways. First in a permutation analysis I examined whether there were any significant clusters of reduced FA within the limbic network ROI. As can be seen in Figure 3, this revealed a significant cluster of decreased FA in the psychosis risk group in the right external capsule, \( p=.008 \).

Second, I further divided the limbic network into four spatially distinct subregions (right and left frontal regions, right and left temporal pole regions) and examined white matter tracts connecting the limbic striatum with each of these four subregions separately. In the white matter tract ROI connecting the limbic striatum with the right frontal subregion, there was a significant difference in FA between the two groups, \( t(35)=2.488, p=0.018 \). In particular, the psychosis risk group exhibited decreased FA in this ROI compared to controls (a follow-up permutation analysis within this ROI revealed a cluster of significantly decreased FA in the right external capsule, \( p=.014 \)). A similar trend was found for the white matter tract ROI connecting the limbic striatum with the left frontal subregion, \( t(35)=1.938, p=.061 \), with decreased FA in the psychosis risk group. In contrast, there were no significant differences between the two groups in FA for white matter tracts connecting the limbic striatum with either right (\( p=.589 \)) or left (\( p=.466 \)) temporal subregions.
Default Mode Network

Next I compared the groups in mean FA in the default mode network white matter ROI. In the default mode WM ROI, there was a trend towards a significant difference in mean FA between the two groups, $t(35)=1.823, p=0.076$. In particular, the psychosis risk group tended to exhibit decreased FA compared to the control group. In the psychosis risk group.

Frontoparietal Network

In the frontoparietal WM ROI, there was no significant difference between groups in mean FA, $t(35)=0.661, p=.512$.

Whole Brain

When analyzing the whole brain white matter skeleton, there was no significant difference between groups in mean FA, $t(35)=1.2576, p=.217$. Furthermore, in a whole brain analysis, I did not find any significant clusters of altered FA between the groups.
Discussion

The current study used DTI to compare white matter integrity in corticostriatal tracts between psychosis risk and healthy controls. This is the first study to specifically examine white matter integrity in corticostriatal tracts, which are theoretically critical in the development of psychosis. I found significantly reduced white matter integrity in tracts connecting the limbic striatum to the limbic cortical network and a trend towards decreased white matter integrity in tracts connecting the default mode striatal region to the default mode cortical network. White matter integrity did not significantly differ between psychosis risk and controls in tracts connecting the frontoparietal striatal region to frontoparietal cortical network. These results add to existing hypotheses for the development of psychosis. Additionally, these results add evidence for reduced white matter integrity as a possible trait marker for psychosis risk.

The current study revealed significantly reduced FA in tracts connecting the limbic striatum to the limbic cortical network. This reduction was most pronounced in a cluster in the right external capsule. To investigate the extent of this finding, I broke the limbic network into 4 subregions by lobe and hemisphere (right and left frontal regions, right and left temporal regions) and examined white matter integrity in tracts connecting limbic striatum to each of these regions. I found reduced white matter integrity in tracts connecting limbic striatum to right frontal limbic network and a trend towards reduced white matter integrity in tracts connecting limbic striatum to left frontal limbic network. White matter integrity did not significantly differ between psychosis risk and controls in tracts connecting the limbic striatal region to either right or left temporal limbic cortical regions. This shows that reduced white matter integrity was limited to frontostriatal tracts.
connecting limbic striatum to the frontal regions of limbic cortical network, and more prominent in the right hemisphere.

These findings highlight the importance of both the limbic striatum and regions of the right frontal lobe in the limbic cortical network (lateral and dorsomedial PFC) in psychosis risk. This is in line with previous findings that highlight the importance of the right PFC in the formation and maintenance of delusions. For example, Coltheart (2010) overviews the two-factor theory of delusion belief, which posits that in order to explain a persistent delusion there must be both (1) an underlying cause to explain the original formation of the delusion belief and (2) an underlying cause to explain the maintenance of the delusional belief and rejection of all evidence to the contrary. Factor 1 may vary across different types of delusions and determine the content of the delusion (e.g., Coltheart discusses a case study in which mirror agnosia (the inability to correctly identify a mirror as a mirror) leads to the delusion of mirror sign (the delusion that your reflection is not yourself)). However, factor 2, improper hypothesis evaluation, is believed to be constant across all delusions as it leads persistence of the delusion by causing the individual to reject any evidence contrary. Neuroimaging studies have shown that right PFC activity corresponds with hypothesis evaluation during several tasks (Fletcher et al., 2001; Turner et al., 2004). Furthermore, performance on these hypothesis evaluation tasks and activity in the right PFC is impaired in FEP (Corlet et al., 2007). This suggests that the right PFC may be critical in the maintenance of delusions.

My findings of reduced white matter integrity in connections between the frontal lobe and limbic striatum are generally consistent with previous research, and support one prominent model of schizophrenia, which conceptualized schizophrenia as arising from
dysfunction related to the limbic striatum. This theory, described above, proposes that
dysfunction of the limbic striatum and its connections with limbic regions, such as
hippocampus and amygdala, and cortical regions, such as PFC, are central in the
development of aberrant salience and psychosis (Grace 2000; Grace, 2016). Furthermore,
it has been found that in rats, D2 antagonists facilitate cortical input to limbic striatum
without affecting input from limbic regions, such as hippocampus and amygdala (Goto &
Grace, 2005). To the extent that we can generalize from this model, this suggests that,
because antipsychotics are D2 antagonists, antipsychotics may reduce psychotic
symptoms by facilitating cortical inputs to limbic striatum. This suggests that psychotic
symptoms may arise from disruption of cortical inputs to the limbic striatum. This is in
line with our findings that these connections between limbic striatum and cortex are
reduced in psychosis risk.

Findings of reduced white matter integrity in the external capsule are also
consistent with previous results. Reduced FA has been found in both chronic
schizophrenia (Bora et al., 2011; Buchsbaum, et al., 1998; Domen et al., 2013) and FEP
(Lee et al., 2013; Mohammad et al., 2016). Additionally, a trend towards reduced FA in
the external capsule has been found in psychosis risk (Carletti et al., 2012). Reductions in
white matter integrity in the external capsule are also seen in other forms of
psychopathology. For example, Scahill and colleagues (2013) found reduced white matter
volume in the external capsule of patients with Huntington’s disease, a neurodegenerative
disease characterized by motor, cognitive, and affective deficits. Symptoms of
Huntington’s disease can also include psychiatric symptoms, including psychotic
symptoms in 9% of cases (Shiwach, 1994). Additionally, Barnea-Goraly and colleagues
(2003) found reduced FA in the external capsule of patients with velocardiofacial syndrome. Velocardiofacial syndrome, also know as 22q11.2 deletion syndrome, as it is caused by a microdeletion on chromosome 22 near location q11.2, is characterized by behavioral and cognitive changes, including a greatly increased risk of psychotic disorders. Specifically, previous research has found that 20-25% of patients with 22q11.2 deletion meet diagnostic criteria for schizophrenia, and up to 30% meet for diagnostic criteria for at least one psychotic disorder (Bassett et al., 2005; Murphy et al., 1999).

These results suggest that reduced white matter integrity in the external capsule may be a trait of psychotic disorders and other neurological disorders that may include psychotic symptoms or increased risk of psychotic disorders. My results are consistent with previous findings of reduced FA in the external capsule in schizophrenia and related neurological disorders. However, the current study is the first study to my knowledge to find significantly reduced FA in the external capsule in psychosis risk.

More generally, my findings of significantly decreased white matter integrity in psychosis risk are in line with previous studies supporting the dysconnectivity hypothesis. The dysconnectivity hypothesis proposes that schizophrenia arises from aberrant structural and functional connectivity between brain regions. This hypothesis is supported by evidence that dysconnectivity is present across stages of psychotic disorders from high risk groups to chronic psychotic disorders (Petterson-Yeo et al., 2011). Additionally, putative genetic risk variants were found to be generally more associated with dysconnectivity between regions than with dysfunction in a specific brain region (Fornito & Bullmore, 2012). While the dysconnectivity hypothesis states that aberrant (increased or decreased) connectivity across many brain regions could lead to psychosis, a review by
Petterson-Yeo (2011) and colleagues found that participants with psychotic disorders were more likely to show reduced connections than increased connections and that findings were most prominent for reduced connections to the frontal lobe. Furthermore, Fornito and colleagues (2013) found that individuals with FEP showed impaired functional connectivity in corticostriatal connections, which was most prominent in frontostriatal connections, and that unaffected relatives showed this same trend to a lesser extent. Thus, Fonrito and colleagues (2013) report that frontostriatal dysconnectivity should be investigated as a possible risk phenotype for psychosis. My results add to the existing literature by providing evidence of reduced structural connectivity in frontostriatal circuits in psychosis risk.

I also found a trend towards reduced decreased white matter integrity in tracts connecting the default mode striatal region to the default mode cortical network. To my knowledge, no previous study has examined white matter integrity in these tracts. However, this trend towards reduced white matter integrity is in line with previous findings of reduced functional connectivity in the default mode in psychosis risk (Jukuri et al., 2013). In fact, in a resting state fMRI study of the same sample as the current study, we have found reduced functional connectivity between the default mode striatal region and default mode cortical network. My results suggest that this reduced functional connectivity may stem from reduced structural connectivity in the form of reduced white matter integrity. However, as this trend did not reach significance in the present study, future research should further examine white matter integrity in these tracts.

I found that white matter integrity did not significantly differ between psychosis risk and controls in tracts connecting the frontoparietal striatal region to frontoparietal
cortical network. Similarly, in the resting state fMRI study of the same sample, discussed above, we found that there were no differences in connectivity between psychosis risk and controls between the frontoparietal striatal region and frontoparietal cortical network. To my knowledge, these studies are the first time that connections between the striatum and the frontoparietal network has been examined in psychosis risk. A study of resting state connectivity in schizophrenia has found that the frontoparietal network was disrupted in patients with schizophrenia (Baker, et al., 2014). However, schizophrenia is a very heterogeneous disorder (e.g., Bannister, 1968). It does typically positive psychotic symptoms. But it also can include negative symptoms, widespread cognitive impairment, and functional disability, all of which may have been absent or mildly present in my psychosis risk sample (Cicero et al., 2014). The current study suggests that psychosis risk specifically may not be associated with decreased striatal-frontoparietal connectivity.

The current study did not identify significantly reduced white matter at the whole brain level of analysis. While many studies of participants with schizophrenia and FEP have found widespread reductions in white matter integrity (Alvarado-Alanis, et al., 2015; Lee et al., 2013), most studies of psychosis risk have not (Carletti et al., 2012; von Hohenberg et al., 2014). There may be several reasons for this. Primarily, reductions in white matter integrity have been shown to worsen throughout the progression of psychotic disorders (Mori et al., 2007). One recent study did not find evidence of overall decreased white matter integrity in schizophrenia until approximately age 35, well after the development of schizophrenia in most cases (Cropley et al., 2017). Hence, the current study seems consistent with other research that widespread white matter dysfunction may
not be present in psychosis risk. Instead, the current study suggests that psychosis risk might be associated with decreased integrity in more specific white matter tracts.

Limitations and Future Directions

The current study has several important limitations. First of all, while FA is a common measure of white matter integrity and sensitive to a variety of microstructural changes, it is not sensitive to the specific type of change. For example, demyelination, axon loss, and edema can all result in decreased FA (Alexander et al., 2007). Additionally, while reduced white matter integrity may emerge as an important trait marker for psychosis risk, reduced white matter integrity itself is not diagnostic of any specific disorder, as a variety of different neuropathologies result in decreased white matter integrity (Lim & Helpern, 2002). However, combined with knowledge of other neuroimaging abnormalities and symptoms, reduced white matter integrity can function as a useful marker. Future studies should continue to combine multiple imaging methods to compare results of DTI analysis with those of resting state and functional MRI or with PET data of dopamine levels for a more complete picture of corticostriatal dysfunction in psychosis risk.

Additionally, our sample consisted of 37 college students—18 at risk for psychosis and 19 healthy controls. The makeup of the sample confers both limitations and strengths onto the current study. Our psychosis risk sample was not recruited from a treatment-seeking population and, as college students, may be more high-functioning than the typical population of individuals at risk for psychosis. This could limit the generalizability of our findings. On the other hand, finding neurological differences in a high-functioning sample, likely at less imminent risk for psychosis than those typically
seeking treatment, implies that these findings are robust enough to appear in the early stages of psychosis risk. Future studies should examine white matter integrity of corticostriatal tracts longitudinally across stages of psychosis risk and see how it may change as symptoms progress.
References


function, a potential mechanism for neuropsychiatric disorders. *Proceedings of the National Academy of Sciences, 104*(19), 8131-8136.


Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data.

*NeuroImage, 31,* 1487-1505.


Figure 1. Striatal (in red) and cortical (in blue) default mode, frontoparietal, and limbic ROIs identified by Choi et al., 2012.
Figure 2. White matter limbic, default mode, and frontoparietal ROIs
Figure 3. Cluster in the external capsule with decreased FA (p<0.05). Peak coordinates (16, 17, -13).
## Appendix 2

### Table of Results

**Previous DTI Findings in Psychosis Risk**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Assessment</th>
<th>Groups</th>
<th>ROI</th>
<th>ROI results</th>
<th>Whole brain results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernard et al.</td>
<td>SIPS</td>
<td>HR (n=26), HC (n=21)</td>
<td>Hippocampal-(-)-thalamic WM tract</td>
<td>ns</td>
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<tr>
<td>2015</td>
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<tr>
<td>Carletti et al.,</td>
<td>CAARMS</td>
<td>HR (n=32), HC (n=32)</td>
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<td>ns</td>
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<tr>
<td>2012</td>
<td></td>
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<tr>
<td>Karlsgodt et</td>
<td>SIPS</td>
<td>HR (n=36), HC (n=25)</td>
<td>ATR, CB, ILF, MTL, SLF, UF</td>
<td>HR &lt; HC in</td>
<td>--</td>
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<tr>
<td>al., 2009</td>
<td></td>
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<tr>
<td>Katagiri et al.</td>
<td>SIPS</td>
<td>HR (n=41), HC (n=16)</td>
<td>--</td>
<td>--</td>
<td>HR &lt; HC in one cluster involving part of the genu and body of CC</td>
</tr>
<tr>
<td>Study</td>
<td>Imaging Technique</td>
<td>Control Group</td>
<td>Region(s)</td>
<td>Results</td>
<td>Note</td>
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<tr>
<td>Mittal et al., 2013</td>
<td>SIPS</td>
<td>HR (n=33)</td>
<td>Superior Cerebral Peduncles (SCP)</td>
<td>ns</td>
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</tr>
<tr>
<td>Peters et al., 2008*</td>
<td>SIPS</td>
<td>HR (n=10), HC (n=10)</td>
<td>AC, AF, DC, UF, genu, and splenium</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Peters et al., 2010*</td>
<td>SIPS</td>
<td>HR (n=17), HC (n=10)</td>
<td>AC, AF, DC, UF, genu, and splenium</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Saito et al., 2017</td>
<td>SIPS</td>
<td>HR (n=46), HC (n=16)</td>
<td>CC: genu, trunk, and splenium</td>
<td>HR&lt;HC in entire CC, genu, trunk, and splenium</td>
<td></td>
</tr>
<tr>
<td>von Hohenberg et al., 2014</td>
<td>SIPS</td>
<td>HR (n=28), HC (n=34)</td>
<td>--</td>
<td>--</td>
<td>ns</td>
</tr>
<tr>
<td>Wang et al., 2016</td>
<td>CAARMS</td>
<td>HR (n=81), HC (n=36)</td>
<td>--</td>
<td>HR &lt; HC in L ATR, L cingulum</td>
<td></td>
</tr>
</tbody>
</table>
CC, L IFOF, L SLF, L UF, and FM

Table 1 only displays FA results, and only examines differences between HR and HC at a single time point. Results for additional groups (e.g. FEP) and results of subgroups (e.g., only HR who later developed psychosis.) are not displayed.

ns designates that an analysis was performed, and yielded nonsignificant results (at p=.05).

-- designates that an analysis was not performed.

Abbreviations used: HR (high risk), HC (healthy controls), L (left), R (right), AC (anterior cingulum), AF (Arcuate fasciculus), ATR (anterior thalamic radiation), CB (cingulate bundle), CC (corpus callosum), DC (dorsal cingulum), FM (forceps minor), IFOF (inferior fronto-occipital fasciculus), ILF (inferior longitudinal fasciculus), MTL (medial temporal lobe), SLF (superior longitudinal fasciculus), UF (uncinated fasciculus)

*These studies included only male subjects