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## Linking optic radiation volume to visual perception in schizophrenia and bipolar disorder

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### ABSTRACT

People with schizophrenia typically show visual processing deficits on masking tasks and other performance-based measures, while people with bipolar disorder may have related deficits. The etiology of these deficits is not well understood. Most neuroscientific studies of perception in schizophrenia and bipolar disorder have focused on visual processing areas in the cerebral cortex, but perception also depends on earlier components of the visual system that few studies have examined in these disorders. Using diffusion weighted imaging (DWI), we investigated the structure of the primary sensory input pathway to the cortical visual system: the optic radiations. We used probabilistic tractography to identify the optic radiations in 32 patients with schizophrenia, 31 patients with bipolar disorder, and 30 healthy controls. The same participants also performed a visual masking task outside the scanner. We characterized the optic radiations with three structural measures: fractional anisotropy, mean diffusivity, and tract volume. We did not find significant differences in those structural measures across groups. However, we did find a significant correlation between the volume of the optic radiations and visual masking thresholds that was unique to the schizophrenia group and explained variance in masking performance above and beyond that previously accounted for by differences in visual cortex. Thus, individual differences in the volume of the optic radiations explained more variance in visual masking performance in the schizophrenia group than the bipolar or control groups. This suggests that individual differences in the structure of the subcortical visual system have an important influence on visual processing in schizophrenia.

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### 1. Introduction

Abnormalities in visual perception have been well-characterized in schizophrenia using various methods (Butler et al., 2008; Green et al., 2009a, 2012; Javitt, 2009; Javitt and Freedman, 2015). Similar types of perceptual dysfunction might also exist in other mental illnesses that share genetic risk factors and clinical characteristics with schizophrenia, including bipolar disorder (Chen et al., 2005; Chkonia et al., 2012; Jahshan et al., 2014). The neural bases of these abnormalities remain largely unknown. Most studies of the visual system in schizophrenia have focused on the cerebral cortex, but some effects observed there

may be downstream reflections of abnormal inputs to the cortical visual system.

The main sensory input pathway to the cortical visual system is from the lateral geniculate nucleus of the thalamus to primary visual cortex (V1). This white matter tract is known as the optic radiations, and its structure can be assessed in vivo using diffusion-weighted magnetic resonance imaging (DWI). Some whole-brain DWI analyses have reported differences in the properties of the optic radiations between schizophrenia or bipolar groups and controls (Douaud et al., 2007; Lee et al., 2014; Mitelman et al., 2007; Versace et al., 2008; Wu et al., 2014). However, those whole-brain studies focused on only one or two measures of optic radiation structure and did not address the possible significance of group differences in the structure of that tract. To our knowledge, only two previous papers have specifically and more comprehensively investigated the structure of the optic radiations in schizophrenia (Butler et al., 2006; Henze et al., 2014). Both found patient-control differences in the structure of the optic radiations, but both had small patient samples ( $N < 20$ ) and used methodologies that

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are no longer current (e.g., lower field strength and angular resolution). There appear to be no published studies specifically examining the structure of the optic radiations in bipolar disorder. Furthermore, no study has linked any structural property of the optic radiations to a performance-based measure of perception in schizophrenia or bipolar disorder.

In this study, we used probabilistic tractography to investigate the optic radiations in schizophrenia, bipolar disorder, and healthy controls. We assessed three DWI-based measures: fractional anisotropy (FA), mean diffusivity (MD), and tract volume. Traditionally, these measures have typically been reported as indirect indices of “white matter integrity,” but the relationships between these measures and the microstructural properties of white matter are now acknowledged to be more nuanced (Jones et al., 2013). Intact, well-organized, well-myelinated axons within a voxel tend to limit diffusion perpendicular to the axons, allowing relatively little diffusion overall and mostly constraining diffusion that does occur to the axis parallel to the axons, making the directionality of diffusion high (Beaulieu, 2002). FA is a measure of the directionality of diffusion; higher FA values indicate that diffusion is more directional. MD is an index of the total amount of diffusion in all directions. Tract volume is a simple measure of the size of a white matter pathway.

When differences in DWI measures between these patient and control groups have been found, FA typically has been lower in schizophrenia and bipolar disorder (e.g., Skudlarski et al., 2013). While MD is less often reported, it is typically higher in those populations (e.g., Clark et al., 2011). Reductions in white matter volume also tend to be found in schizophrenia and bipolar disorder (e.g., Oertel-Knöchel et al., 2015). Therefore, we expected that FA and tract volume would be reduced in schizophrenia and bipolar disorder, while MD would be higher in the patient groups, compared to controls. We also examined correlations between each DWI measure and visual masking performance within each group.

## 2. Methods

### 2.1. Participants

Participants in this study came from a larger, ongoing, NIMH-sponsored study of visual processing in major mental illness. The sample included 32 patients with schizophrenia, 31 bipolar disorder patients, and 30 healthy controls. All patient participants were clinically stable outpatients with a DSM-IV diagnosis of either schizophrenia or bipolar disorder who were not in a current mood episode. Healthy participants were a matched community sample. Full details about participant selection criteria and recruitment, are included in the Supplementary Methods.

Patients' clinical symptoms were characterized using the Brief Psychiatric Rating Scale (BPRS), Young Mania Rating Scale (YMRS), and Hamilton Depression rating scale (HAM-D) (Hamilton, 1960; Overall and Gorham, 1962; Thompson et al., 1994; Ventura et al., 1993; Young et al., 1978). The study used the 24-item version of the BPRS developed at the UCLA Clinical Research Center for Schizophrenia and Psychiatric Rehabilitation, in which each item is rated on a scale of 1 to 7, and the 21-item version of the HAM-D scale (Hamilton, 1960; Overall and Gorham, 1962; Ventura et al., 1993).

### 2.2. MRI data collection

All MRI data was collected at the UCLA Staglin Center for Cognitive Neuroscience on a 3-Tesla Siemens Tim Trio scanner with a 12-channel head coil (Siemens Medical Solutions; Erlangen, Germany). T1-weighted structural scans were collected using a Magnetization-Prepared Rapid Gradient Echo (MPRAGE) sequence (1.9 s TR, 3.4 ms TE, 9° flip-angle, 1 mm isotropic voxels, 256 × 256 × 160 voxel field of view). DWI scans were collected with 64 diffusion directions at a B-value of

1000 s/mm<sup>2</sup> (8 s TR, 93 ms TE, 2.3 mm isotropic voxels, 96 × 96 × 58 voxel FOV).

### 2.3. MRI processing

DWI data were preprocessed, and FA and MD measures calculated for each voxel, using a well-documented standard FSL pipeline (Jenkinson et al., 2012; Smith et al., 2004). Thalamus and V1 region masks were created from automated FreeSurfer reconstructions of each participant's T1 anatomical scan (Dale et al., 1999; Fischl et al., 1999). We used a standard approach and parameters recommended by the FSL developers to perform bidirectional tractography between these two region masks in each hemisphere with FSL (Behrens et al., 2007, 2003). The results of this tractography analysis were thresholded according to the number of streamlines passing through each voxel and other criteria (see Supplementary Methods) to create a unique volumetric mask of the optic radiations for each participant. A detailed description of all steps and parameters used to process the MRI data is in the Supplementary Methods. Mean FA and MD within the optic radiations were computed by averaging FA and MD scores within the mask of all tract voxels in each hemisphere, then averaging across hemispheres. The volume of the optic radiations, in mm<sup>3</sup>, was calculated based on the final, bilateral, optic radiation mask of each participant (see Supplementary Methods).

### 2.4. Masking task

In a separate testing session without MRI, participants' visual perception was assessed with a task in which they attempted to identify backward-masked objects from one of six categories of household items. For each participant, we estimated the length of the delay at which that person would be able to identify the type of object correctly 50% of the time, using standard psychometric curve-fitting methods (Prins and Kingdom, 2009; Wichmann and Hill, 2001). These analyses are described in detail in the Supplementary Methods. Threshold ISIs were used for correlations with DWI measures.

## 3. Results

Demographic and clinical characteristics of the sample, as well as group comparisons of those variables, are in Table 1. There were no significant differences in age, handedness, or parental education across the three groups, and the two patient groups did not differ in the number of years since their diagnosis. The groups did differ significantly in gender and years of personal education. The two patient groups also differed significantly in the number of individuals taking antipsychotic and mood stabilizing medication, and in antipsychotic medication dosage. Schizophrenia patients had higher scores on the BPRS than bipolar patients, but the two patient groups did not have significantly different scores on the YMRS or HAM-D. A one-way ANOVA comparing backward masking thresholds did not show a significant difference across groups ( $F(2,82) = 2.16, p = 0.12$ ). Means (standard deviations) were similar across groups for the masking thresholds: schizophrenia = 58.30 (20.90) ms, bipolar = 48.68 (20.17) ms, controls = 60.18 (24.09) ms.

Fig. 1 shows an example unilateral optic radiation tract mask, and the FA values of voxels within it. Across subjects, FA, MD, and tract volume were all normally distributed, so we compared those measures across groups using ANOVAs. Descriptive and inferential statistics for each ANOVA are in Table 2. Because there was a significant gender difference across the three groups, we included gender as a factor in the ANOVAs. There were no significant main effects of group, nor group-by-gender interactions, for any of the three DWI measures.

We examined the associations between visual masking thresholds and the three DWI measures in each of the three participant groups. A Bonferroni-corrected  $\alpha$ -level of 0.005 was used for the correlations. As

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