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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

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Contributors: MFG is PI of the larger project from which the present data came. EAR initiated the current project and developed the strategy for the analyses in consultation with JL, JKW, KLN, and MFG. SNN preprocessed the data and EAR performed the rest of the data analysis. Together, EAR, JL, JKN, KLN, SAE, and MFG interpreted the results. EAR wrote the manuscript with input from the other authors. All authors contributed to and approved the final manuscript.

Conflicts of interest: Dr. Green has been a consultant to AbbVie, ACADIA, DSP, FORUM, Lundbeck, and Takeda. He is on the Scientific Board of Luc and has received research support from Amgen and Forum. All other authors report no potential conflicts of interest.

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.

Keywords

Schizophrenia; Bipolar Disorder; Diffusion Weighted Imaging; Tractography; Optic Radiations; Visual Perception

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 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 mostlu 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 sec TR, 3.4ms TE, 9 flip-angle, 1mm isotropic voxels, 256 x 256 x 160 voxel field of view). DWI scans were collected with 64 diffusion directions at a B-value of 1000 s/mm^2 (8sec TR, 93ms TE, 2.3 mm isotropic voxels, 96x96x58 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^3, 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.

Figure 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 α-level of 0.005 was used for the correlations. As shown in Figure 2, tract volume was significantly correlated with masking thresholds, but only in the schizophrenia group (schizophrenia $r(29) = -0.584$, $p = 0.001$; bipolar $r(26) = 0.037$, $p = 0.857$; controls $r(29) = -0.052$, $p = 0.784$). Indeed, follow-up Fisher's r-to-z comparisons of correlation magnitudes showed that the correlation between tract volume and masking thresholds was significantly larger in the schizophrenia group than the other groups (schizophrenia vs. bipolar $Z = 2.46$, $p = 0.01$; schizophrenia vs. controls $Z = 2.24$, $p = 0.03$).

Neither FA nor MD was correlated with masking performance in any of the three groups. FA correlations were as follows: schizophrenia $r(29) = -0.297$, $p = 0.118$; bipolar $r(26) = 0.107$, $p = 0.602$; controls $r(29) = -0.193$, $p = 0.307$. MD correlations were: schizophrenia $r(29) = 0.227$, $p = 0.236$; bipolar $r(26) = 0.051$, $p = 0.804$; controls $r(29) = 0.038$, $p = 0.841$.

4. Discussion

Contrary to our expectations, we found no evidence of group differences in FA, MD, or volume of the optic radiations across patients with schizophrenia, patients with bipolar disorder, and healthy controls, even though differences in FA have been reported in previous studies. Our sample was larger than those in many previous reports, and our scanning and analysis techniques took advantage of numerous recent methodological advances. These methodological differences could be related to the difference between our findings and those of previous studies.

Although we found no group differences in the properties of the optic radiations between patients and controls, we did find a significant correlation between tract volume and perceptual performance in schizophrenia. To our knowledge, this is the first time that the structure of a subcortical visual pathway has been linked to performance on a visual masking task in schizophrenia. This result suggests that individual differences in brain structure as early as the optic radiations may have cascading effects on perception in the disorder. The specificity of the link between neuroanatomical structure and perceptual performance to the schizophrenia group suggests that there is a different relationship between the structure of the optic radiations and perception in schizophrenia than in bipolar disorder or healthy controls. Specifically, individual differences in the volume of this tract appear to matter more for the perception of masked stimuli in the schizophrenia group than in the other groups.

We recently identified another neuroanatomical correlate of performance on the same masking task in an overlapping sample of participants. In that study, we found that the thickness of visual cortex was significantly correlated with masking thresholds in schizophrenia patients (Reavis et al., 2016). To determine whether optic radiation volume accounts for additional variance in schizophrenia patients' masking performance, above and

beyond that explained by cortical thickness, we performed a multiple regression. Specifically, we added optic radiation tract volume to thickness of early visual cortex in a stepwise regression model. We found that adding the tract volume measure accounted for significantly more variance in masking performance than cortical thickness alone (ΔF (1,26)=14.34, Δr^2 = 0.27, p=0.001). Thus, these two neuroanatomical features appear to have non-overlapping influences on visual perception in schizophrenia. Together, optic radiation volume and the thickness of visual cortex accounted for about half of the variance in schizophrenia patients' performance on the masking task (F(2,26)=13.24, r^2=0.51, p < 0.001). The surprising ability of just two neuroanatomical features of the early visual system to account for such a large amount of perceptual variance raises the possibility that individual differences in the structure of the early visual system have profound effects on the way people with schizophrenia experience the visual world.

The present study had several limitations. First, there was an imbalance in the gender distribution of the participant groups. Although we found no effects of gender in our analyses, a more balanced distribution of gender across groups would be desirable in future studies. Second, there were no significant differences in visual masking performance between the groups. Many previous studies have found visual masking deficits in schizophrenia, and it is unclear why such differences were not apparent in this sample. On the positive side, the lack of group differences in masking makes the interpretation of correlational differences between groups clearer. Third, patients were on clinically-determined doses of medication. To rule out any possible medication effects, it would be informative to test participants who have never received psychotropic medication (e.g., first episode patients). Fourth, current tractography methods cannot differentiate the optic radiations proper from adjacent pathways that connect other thalamic nuclei (e.g., pulvinar) to V1.

Despite these limitations, the results of this study suggest that perception is more strongly influenced by the structure an early visual pathway in schizophrenia than in bipolar disorder or healthy controls. This is consistent with the possibility that some of the differences in the function of the cortical visual system which have been reported between schizophrenia patients and controls (e.g., Green et al., 2009b; Silverstein et al., 2015; Yoon et al., 2008) might be downstream effects related to individual differences in inputs from the subcortical visual system. It will be important for future work to investigate how such individual differences in the structure of early visual areas might relate to individual differences in the function of those areas in schizophrenia. It also remains an important question to what extent these individual differences in the structure (and perhaps function) of early visual areas are correlated with performance on other measures of perception and cognition, as well as disease characteristics (e.g., symptoms). Processing in many cognitive domains depends on accurate perceptual input (Javitt and Freedman, 2015), and cognition is a major determinant of outcomes in schizophrenia (Green, 1996; Green et al., 2000). Thus, it is conceivable that individual differences in the structure and function of early visual areas could have wide-ranging effects in the disorder. Fortunately, the structure and physiology of the early visual system is well-understood in healthy populations, making investigation of the early visual system in schizophrenia an especially promising topic for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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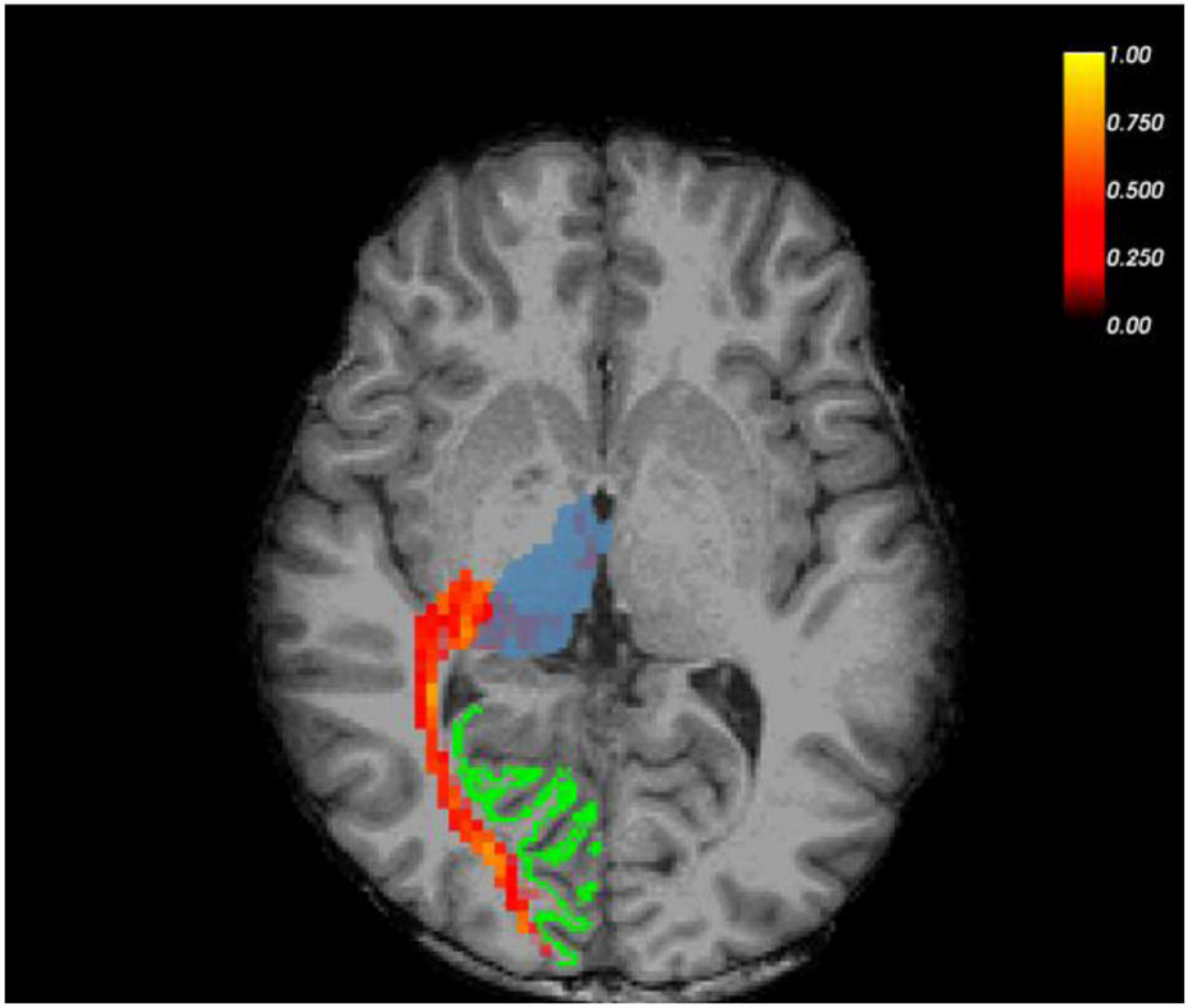

Figure 1.
Example right-hemisphere optic radiation tract and seed masks in a healthy control participant, overlaid on that participant's high-resolution anatomical scan (T1). Thalamus mask is in blue, V1 mask in green. Thresholded FA map is in red/yellow; brighter colors indicate higher FA.

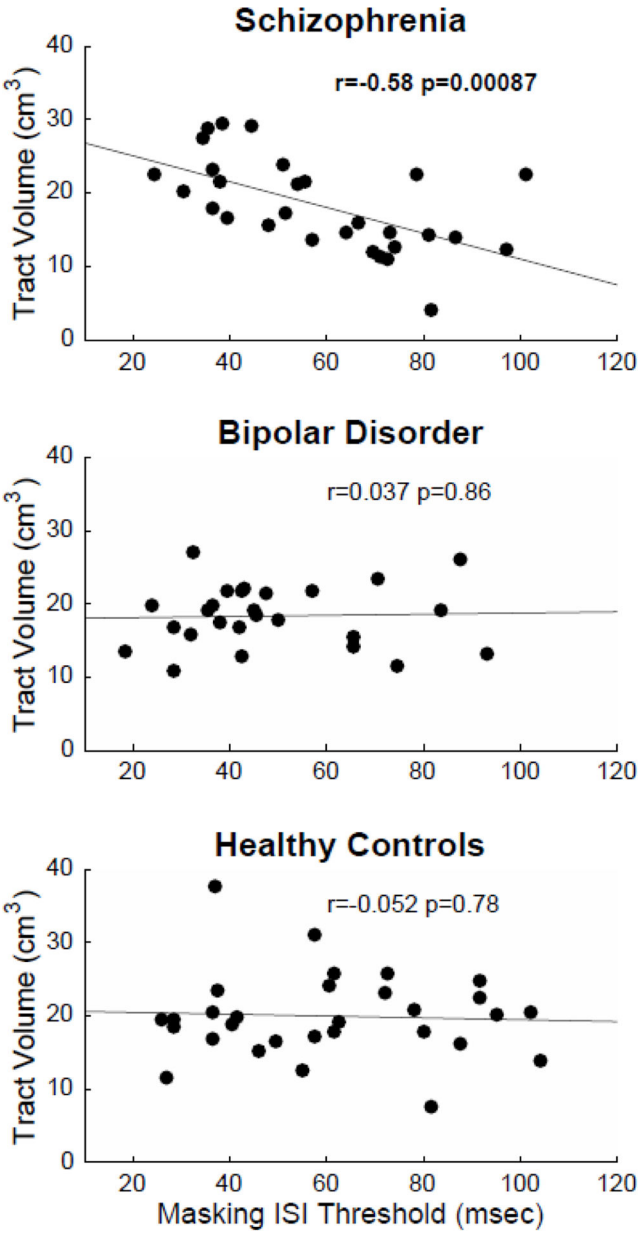

Figure 2.
Correlations between masking thresholds tract volume for each group.

Table 1

Characterization of participants.

	SZ Patients (N=32)	BD Patients (N=31)	Controls (N=30)	Group Comparison	
	Mean (SD)	Mean (SD)	Mean (SD)	Statistic	*p*
Age	44.66 (12.44)	43.74 (13.15)	48.00 (6.54)	$F(2,90)=1.23$	$p=0.30$
Illness Duration	23.91 (13.51)	22.50 (12.61)		$t(58)=0.42$	$p=0.68$
Education	12.81 (1.94)	13.94 (2.34)	14.33 (1.83)	$F(2,90)=4.64$	$p=0.01$
Parental Education	12.88 (2.56)	13.83 (2.74)	13.43 (3.01)	$F(2,82)=0.86$	$p=0.43$
Gender (M/F)	23 / 9	13 / 18	15 / 15	$X^2(2)=6.12$	$p=0.05$
Handedness (R/L)	27 / 5	27 / 4	26 / 4	$X^2(2)=0.11$	$p=0.95$
BD Type: I / II		20 / 11			
BPRS (Total)	40.47 (12.23)	32.77 (9.09)		$t(61)=2.83$	$p=0.01$
HAM-D (Total)	7.38 (6.26)	7.26 (4.61)		$t(61)=0.08$	$p=0.93$
YMRS (Total)	5.06 (3.93)	4.06 (5.02)		$t(61)=0.88$	$p=0.38$
Antipsychotic medication (Y/N)	28 / 4	20 / 11		$X^2(1)=4.59$	$p=0.03$
CPZ-equivalent dosage (mg/day)	516.15 (407.08)	257.60 (160.03)		$t(33)=2.32$	$p=0.03$
Mood stabilizer frequency (Y/N)	10 / 23	23 / 8		$X^2(1)=12.33$	$p=0.01$

Table 2

Above: Means (standard errors) of DWI measures by group. Below: ANOVA statistics for each DWI measure.

	Schizophrenia	Bipolar Disorder	Healthy Controls
FA (ratio)	0.432 (0.004)	0.428 (0.004)	0.427 (0.004)
MD (μm^2/sec)	79.182 (0.703)	81.169 (0.651)	81.213 (0.653)
Tract Volume (cm^3)	18.488 (1.098)	17.692 (1.016)	19.976 (1.020)

	Main effect: Group	Main Effect: Gender	Interaction: Group-by-Gender
	df_{within} = 2 df_{error} = 87	df_{within} = 1 df_{error} = 87	df_{within} = 2 df_{error} = 87
FA	F = 0.392 p = 0.677 η^2_p = 0.009	F = 0.278 p = 0.599 η^2_p = 0.003	F = 0.855 p = 0.429 η^2_p = 0.019
MD	F = 2.858 p = 0.063 η^2_p = 0.062	F = 0.734 p = 0.394 η^2_p = 0.008	F = 2.761 p = 0.069 η^2_p = 0.060
Tract Volume	F = 1.292 p = 0.280 η^2_p = 0.029	F = 0.606 p = 0.438 η^2_p = 0.007	F = 0.414 p = 0.662 η^2_p = 0.009