Published in final edited form as:

Schizophr Res. 2018 March ; 193: 276–283. doi:10.1016/j.schres.2017.06.062.

White matter microstructure predicts cognitive training-induced improvements in attention and executive functioning in schizophrenia

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Abstract

We examined the relationship between white matter microstructure in schizophrenia using diffusion tensor imaging (DTI) and cognitive improvements induced by 70 hours (~16 weeks) of cognitive training. We measured anatomical connectivity in 48 patients with schizophrenia (SZ) and 28 healthy control participants (HC) at baseline, and then examined the relationship between anatomical connectivity at baseline and training-induced cognitive gains in 30 SZ who performed diffusion imaging after completing 70 hours of training. Compared with healthy control participants, individuals with schizophrenia showed reduced white matter integrity at baseline, as indexed by fractional anisotropy metrics, in bilateral posterior corona radiata, bilateral retrolenticular internal capsules, bilateral posterior thalamic radiation, left anterior corona radiata, left superior longitudinal fasciculus, left sagittal stratum, right cerebral peduncle and the genu and splenium of the corpus callosum. After training, schizophrenia participants showed significant gains in attention/vigilance, speed of processing, verbal learning, visual learning and executive functioning. White matter integrity within the right fronto-occipital fasciculus predicted training-induced improvements in attention/vigilance, while white matter integrity within the right corticospinal tract and bilateral medial lemnisci predicted cognitive training-induced

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Contributors

Author Karuna Subramaniam acquired, analyzed and interpreted the DTI data, and wrote the manuscript. Author Jeevit Gill helped with the analyses of the DTI data. Author Melissa Fisher helped with the analyses of the neurocognitive data. Author Pratik Mukherjee assisted with DTI MRI protocol set up and implementation. Author Srikantan Nagarajan assisted with the analyses and interpretation of the results of the study. Author Sophia Vinogradov revised the manuscript and assisted with the interpretation of the findings of the study.

Conflict of interest

None of the authors have any conflicts of interest to declare.

improvements in executive functioning, areas that did not show white matter tract deficits at baseline. These findings suggest that preserved white matter integrity connecting long-range prefrontal-thalamic-sensorimotor areas may be an important determinant for training-induced neurocognitive plasticity.

Graphical abstract

Introduction

Schizophrenia is considered a disorder of both functional and structural neural system connectivity, with widespread deficits observed in white matter architecture (Marenco et al., 2012; Rubinov & Bassett, 2011; Kubicki et al., 2003; 2005). In white matter, diffusion is restricted by the axon, such that water molecules are more likely to move parallel to the axon than perpendicular to it. This results in a diffusion anisotropy (where diffusion is not equally distributed) along the axon. An index known as fractional anisotropy (FA) is used to characterize this anisotropy and is thought to be one measure of white matter integrity (Karlsgodt et al., 2008; Skudlarski et al., 2010; Klingberg, 2006). Reduced white matter integrity, as indexed by decreased fractional anisotropy (FA), has been observed in patients with schizophrenia (SZ), relative to healthy control (HC) participants, in whole brain white matter (Lim et al 1999), as well as various regions such as within prefrontal white matter (Buchsbaum et al 1998), in the splenium of the corpus callosum (Foong et al 2000), in the uncinate fasciculus connecting the frontal and temporal lobe (Kubicki et al., 2002), in the cingulum (Kubicki et al., 2003), and in frontal and occipital areas (Kumra et al., 2004; Minami et al., 2003). Deficits in white matter integrity have also been found during early stages of the illness (Kumra et al., 2004), suggesting that it may be related to fundamental aspects of pathophysiology.

Although several studies have conducted assessments on both white matter integrity (i.e., FA measures) and clinical/cognitive measures (Buchsbaum et al., 1998; Foong et al., 2000; Kubicki et al., 2002; Wolkin et al., 2003; Kubicki et al., 2003; Marenco et al., 2012; Wagner et al., 2015), only some of these studies have found significant correlations between white matter integrity (i.e., indexed by fractional anisotropy (FA) and cognition in schizophrenia (SZ) patients (Kubicki et al., 2002; 2003; Karlsgodt et al., 2008; Mamah et al., 2010; Marenco et al., 2012; Wagner et al., 2015). For example, Mamah et al (2010) found SZ

patients had reduced FA in the anterior limb of the internal capsule (the medial portion of which includes the anterior thalamic radiation), with better integrity being associated with better working memory and executive functioning. Marengo et al (2012) found reduced thalamocortical connectivity in SZ patients compared to HC subjects, with greater thalamic-prefrontal connectivity being associated with better fMRI working memory signal and working memory performance. Finally, Wagner et al (2015) recently showed reduced FA in right anterior limb of the internal capsule (ALIC), right thalamus and corpus callosum in SZ. FA in right ALIC correlated with thalamic fMRI signal across both a congruent Stroop attention task and an incongruent Stroop executive functioning task. Greater FA in right ALIC also correlated with Stroop executive functioning performance and with better frontal-thalamic effective connectivity in SZ. Together, these studies suggest that SZ is characterized by abnormal structural and functional connections (Andreasen et al, 1996; Pergola et al., 2015), and that greater integrity of thalamic-prefrontal connections, in particular, may be important for better cognition in schizophrenia.

In a meta-analysis, Ramsay et al (2015) showed that cognitive remediation training was associated with increased activity in prefrontal and thalamic regions, in which prefrontal and thalamic regions partially overlapped with these regions being previously identified in other meta-analytic studies as showing working memory and executive functioning deficits in schizophrenia. In another study, cognitive training enhanced functional thalamo-prefrontal connectivity, such that it became correlated with overall improved cognition (Ramsay et al., 2016). We and others have also shown that cognitive training can induce plasticity in prefrontal functional activation patterns such that increased prefrontal signal became correlated with behavioral gains (Bor et al., 2011; Haut et al., 2010; Subramaniam et al., 2012; 2014; Wexler et al., 2000; Wykes et al., 2002). These findings indicate that while schizophrenia patients appear to show thalamocortical dysfunction, cognitive training may drive plasticity particularly within thalamocortical areas via enhancement of functional activity dependent mechanisms. Therefore, for cognitive training to be successful, there has to be intact white matter connectivity, particularly between thalamus and prefrontal cortex, so that the activity dependent neural processes can get propagated for efficient long-range signal transmission that supports attention, working memory and executive functions.

In order to investigate this question, we obtained Fractional Anisotropy (FA) metrics to quantify white matter integrity at baseline in 28 healthy control (HC) subjects and 48 participants with schizophrenia (SZ) who had enrolled in a trial of 70 hours of intensive cognitive training over a period of approximately 16 weeks. Our cognitive training protocol was designed to intensively target impairments in lower level attention/perceptual processing as well as higher-order working memory and executive operations (Adcock et al., 2009; Fisher et al., 2009; Fisher et al., 2017; Mahncke et al., 2006). The training-induced cognitive gains of the larger clinical trial can be found in Fisher et al (2017). Briefly, in this larger clinical trial, training-induced cognitive gains after 70 hours compared to baseline were found in: attention, speed of processing, visual learning, verbal learning and executive functioning/problem solving. In the present study, we investigated the association between baseline FA and these significant training-induced cognitive improvements.

Methods

Participants

Forty-eight clinically stable volunteer schizophrenia (SZ) patients who were willing to undergo diffusion MRI, were recruited from our randomized clinical trial of cognitive training in schizophrenia ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02105779) NCT02105779). The 48 SZ participants who underwent diffusion MRI were matched to 28 healthy comparison participants (HC) at a group level on age and gender (Table 1). The SZ range was from 25 to 61 years, and the HC range was similar, from 23 to 60 years. SZ patients were chronically ill for over 20 years (mean illness duration = 24.52 years). SZ participants were recruited from community mental health centers and outpatient clinics, and HC subjects were recruited via advertisement. Inclusion criteria for the diffusion MRI study were Axis I diagnosis of schizophrenia, schizoaffective disorder, or psychosis not otherwise specified (NOS) (determined by the Structured Clinical Interview for DSM-IV [SCID]) (First et al., 2002), or, for HC subjects, no Axis I or Axis II psychiatric disorder (SCID—Nonpatient edition), no substance dependence in the past 12 months or current substance abuse, good general physical health, no neurological disorder, age between 18 and 60 years, no claustrophobia, no metal in the body, and English as first language. All subjects gave written informed consent. HC participants did not undergo any training. Altogether 111 SZ patients were randomized in our larger clinical trial (some of whom did not meet MRI criteria or were unwilling to take part in the diffusion MRI study). Clinical and neuropsychological assessments were conducted at baseline, and after each module of training. Prior to study entry, all SZ subjects had outpatient status for 3 months and stable doses of psychiatric medications for at least 4 weeks (Table 2).

SZ subjects were stratified by age, education, gender, and symptom severity and randomly assigned to either: 1) 40 hours of auditory processing exercises followed by 30 hours of visual processing exercises (Targeted Cognitive Training Condition, TCT, N=25); or, 2) 40 hours of auditory processing exercises that included 10 hours of training in auditory social cognition exercises, followed by 30 hours of visual processing exercises that included 10 hours of visual social cognition exercises (Targeted Cognitive Training plus Social Cognition Training (TCT+SCT, N=23). SZ subjects were blind to group assignment. Both groups received a total of 70 hours of training over a period of 16 weeks. During the course of training, 8 TCT and 10 TCT+SCT out of the 48 SZ participants who completed diffusion MRI at baseline withdrew from the study, leaving 30 SZ completers who performed diffusion imaging after 70 hours of training.

Targeted Cognitive Training

Targeted cognitive training was provided by software developed by PositScience, Inc. In the general auditory and visual processing exercises, participants were driven to make progressively more accurate distinctions about the spectro-temporal fine-structure of auditory and visual stimuli under conditions of increasing working memory load (i.e. increasing number of stimuli, and decreasing inter-stimulus intervals and duration of stimulus presentation). In the auditory exercises, stimuli across the exercises spanned the acoustic and organizational structure of speech, from very simple acoustic stimuli and tasks

(e.g., time order judgments of rapidly successive frequency modulated sweeps) to the complex manipulations of continuous speech (e.g., narrative memory) (Fisher et al., 2009; Fisher et al., in press). In the visual exercises, stimuli ranged from simple visual sine-wave sweeps to more complex and ecologically-meaningful visual stimuli such as birds, or cars and road signs. The tasks in the visual exercises ranged from simple perceptual attention discrimination tasks (e.g. discriminate direction of visual sweeps), to more complex tasks requiring multiple object tracking, divided attention, and spatio-temporal working memory and executive functioning (Surti et al., 2011).

Both auditory and visual exercises were continuously adaptive in that they first established the precise parameters within each stimulus set required for an individual participant to maintain 80% correct performance; once that threshold was determined, task difficulty increased or decreased systematically and parametrically as performance improved or declined. These same principles were applied in the second training module, focused on the visual system. The design and implementation of this approach was informed by research demonstrating impairments in schizophrenia in basic auditory and visual perceptual and attention processes, as well as in higher-order working memory, and executive functions (e.g., Green, 1996; Javitt et al., 2000; Javitt, 2009). All TCT exercises are listed in Table 3.

Social Cognitive Training

Social cognitive training (SCT) was provided by the SocialVille program, an online (browser) program developed by PositScience, designed to treat social cognition deficits in schizophrenia (Nahum et al., 2014). SCT training in the current study consisted of 9 exercises, which targeted perception, attention and memory in the social cognitive domains of vocal and visual affect perception and visual social cue perception (gazes and faces).

The SCT exercises employ socially-relevant stimuli and discriminations with the goal of improving speed and accuracy in brain systems dedicated to the processing of social information (e.g., Nahum, Lee, & Merzenich, 2013). Participants are driven to make progressively more accurate discriminations in socially-relevant features such as prosodic fluctuations (auditory domain), and faces, facial expressions, and gaze directions (visual domain). For example, in a facial expression exercise, the users are required to find a matching emotional expression to that of a rapidly presented target face. All SocialVille exercises used in the study are listed in Table 4.

Clinical and Cognitive Assessments

SZ subjects received clinical and cognitive assessments at baseline and after 40 and 70 hours of training. Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987), which rates each symptom on a scale of 1 (absent) to 7 (extreme). Cognition was assessed with the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008). All tests were scored and re-scored by a second staff member blind to the first scoring. All cognitive outcome measures were distinct and independent from tasks practiced during training.

Behavioral Statistical Analyses

Repeated-measures ANOVAs were conducted to investigate clinical (assessed with the PANSS) and cognitive change (assessed with the MCCB) in the patients who completed 70 hours of training when compared to baseline. To increase our power for finding a relationship between FA metrics and training outcomes, we combined the behavioral analyses across the two training groups. Pearson's two-tailed correlations were used to investigate the association between baseline white matter integrity (i.e., fractional anisotropy) and only the MCCB measures in which SZ patients showed significant cognitive training-induced improvements after training when compared to baseline. To protect against Type 1 errors, we minimized the number of correlations tested that we implemented from a priori specific hypotheses by only examining tracts in which baseline FA predicted significant training-induced cognitive improvements. Therefore, after having limited the number of correlations tested in the first place, these brain training-induced behavioral correlations were not corrected for multiple comparisons corrections, as this would be overly conservative, and inflate the Type 2 error rate (i.e., increase the chance of missing true effects in the brain) as a result of overcorrecting for multiple tests.

MRI Protocol

Whole-brain structural MRI data were acquired using a 3T Siemens (3Tesla, 3D sequence, flip angle 9°, TE 2.98 ms, TR 2300 ms, TI 900 ms, FOV 256 × 256 mm, matrix 256 × 256 × 252, NEX = 0.5, voxel dimensions 1×1×1 mm, slice thickness=1, slices per tab=160, acquisition time = 4:54 min.

Diffusion data were acquired using a 2D axial diffusion Spin Echo sequence. 35 different diffusion directions were used with $b = 800 \text{ s/mm}^2$ and 5 $b = 0 \text{ s/mm}^2$ reference images (TE=84ms, TR=9000ms, FOV=256×256mm², matrix=64×64, in-plane voxel dimensions=3×3mm², slices=72, slice thickness= 2mm, acquisition time= 5.42mins).

Whole-brain Fractional Anisotropy Analyses

FA images were analyzed using Tract Based Spatial Statistics (TBSS) in FSL. Diffusion-weighted images were corrected for distortions induced by eddy currents (Studholme et al., 1997) and registered to the non-diffusion weighted volume ($b = 0$) with six degrees of freedom transformation to correct for head movements. The DT was estimated on a voxel-by-voxel basis using the DTIfit tool-box, part of the FMRIB Diffusion Toolbox within FSL (FSLv4.1.7; <http://www.fmrib.ox.ac.uk/fsl/>) in order to obtain FA maps. Diffusion data was then transformed to Montreal Neurological Institute (MNI) space, the following procedure was performed: (i) DTI images were aligned to the template in MNI space using the FMRIB's linear image registration tool with 12 degrees of freedom, (ii) the non-linear transformation to the template was computed using the FMRIB's non-linear image registration tool (FNIRT) entering the information from the linear transformation and obtaining a coefficient file with both the linear and non-linear component of the transformation to MNI space, (iii) inverse transformations were calculated from the coefficient file obtained from FNIRT.

A study-specific skeleton for the FA maps (which represents the center of all fiber bundles in common to all subjects) was generated using an optimal FA threshold of 0.2 following visual inspection. Each subject's aligned FA map was projected onto this skeleton and then entered into voxel-wise cross-subject statistics. A general linear model was used to test FA differences between the schizophrenia patients and the healthy control participants using the FSL randomise tool, with two contrasts (patients vs. controls and controls vs. patients) using permutation testing (5000 random permutations) applied to the general linear model. Statistical FA maps were thresholded at $p < 0.05$ FWE corrected, with multiple comparisons correction at a cluster level using the TFCE (the threshold-free cluster enhancement) approach. The John Hopkins University (JHU) white matter tractography international consortium for brain mapping (ICBM)-DTI-81 white matter labels atlas was used to identify the names of white matter tracts containing the clusters of significant between-group differences (Wakana et al., 2007; Hua et al., 2008). The FA values within the skeleton mask within each tract were computed for each participant and averaged across all the tracts for each participant in order to compute group differences in global FA throughout the brain (TFCE with FWE $p < .05$ correction).

Results

Training-induced cognitive changes

In the larger clinical trial, we found significant main effects of training in attention, speed of processing, verbal learning, visual learning, executive functioning/problem solving (Fisher et al., 2017). Global cognition (which was computed as a composite of all the MCCB scores), also showed a main effect of training in the larger clinical trial (Fisher et al., 2017) but was not used in the present analysis as this measure does not assess a specific cognitive function, but is rather derived from the other MCCB measures. Within these cognitive measures that showed training-induced improvements, baseline FA only correlated with significant improvements in the MCCB outcome measures of attention/vigilance, as measured by the Continuous Performance Task-Identical Pairs (CPT-IP) and executive functioning, as measured by NAB Mazes. We did not find a significant reduction in overall clinical symptoms, positive symptoms, negative symptoms or disorganized symptoms after 70 hours of cognitive training when compared to baseline (all p 's $> .05$).

Whole-brain voxel-based analyses of fractional anisotropy (FA) group differences at baseline

When we averaged FA values within the skeleton mask across all the tracts for each participant in order to compute group differences in global FA throughout the brain, SZ patients revealed marginally lower global FA than HC participants ($F[1,74]=3.29$, $p=.07$). Further, TBSS whole brain analyses revealed widespread white matter abnormalities in SZ patients within a network of tracts (surviving multiple comparisons correction TFCE, $p < .05$ FWE-corrected) (see Table 5, Figure 1). Specifically, the SZ group showed significantly lower FA compared to the HC participants in: (i) bilateral posterior corona radiata, (ii) bilateral retrolenticular portion of the internal capsules, (iii) bilateral posterior thalamic radiations, (iv) left anterior corona radiata, (v) left sagittal stratum (vi) left superior longitudinal fasciculus, (vii) right cerebral peduncle (viii) genu of the corpus callosum and

(ix) splenium of the corpus callosum (Figure 1). The schizophrenia group did not show any regions of significantly greater FA than controls. Finally, all significant group differences in FA values had medium to large effect sizes (Table 5). There was no correlation of baseline FA measures of connectivity with age, years of education, or with chlorpromazine equivalents (all p 's > .05 with multiple comparison correction).

White matter structural integrity and training-induced gains in attention and executive functioning

Next, we examined the association between baseline measures of white matter structural integrity and significant gains in cognitive outcome measures in the SZ participants. We found a significant association between improved performance in the CPT-IP attention/vigilance task and FA within the right superior fronto-occipital fasciculus ($r(28)=.52$, $p=.004$) (Figure 2). We also found a significant correlation between improved executive functioning performance on NAB Mazes and FA within right corticospinal tract (right CST: $r(28)=.37$, $p=.05$) and bilateral medial lemnisci (left MLN: $r(28)=.40$, $p=.03$; right MLN: $r(28)=.43$, $p=.02$) (Figure 2). None of these regions showed a significant decrease in white matter integrity at baseline in SZ as compared to HC participants (Figure 2). We did not find any significant correlations between baseline FA measures in these tracts and baseline MCCB measures of attention/vigilance or executive functioning in SZ participants (all p 's > .05). We also did not find significant correlations between baseline measures of radial, axial or mean diffusivity with training-induced gains in attention or executive functioning (all p 's > .30). It also must be noted that we found no differences between the TCT vs. SCT groups in either baseline FA (fronto-occipital, CST, medial lemnisci; all p 's > .10) or behavioral change (on either attention or executive functioning; all p 's > .40) after 70 hours of training vs. baseline in the present study. There was also no group by time interaction found in the larger study (Fisher et al., 2017) in any of the cognitive measures tested. Taken together, regardless of whether we combined the groups or separated the SZ group into TCT and SCT, we still found intact FA at baseline in each SZ group when compared to the HC group within the 3 tracts (fronto-occipital, CST, medial lemnisci) in which baseline FA predicted significant training responsivity on attention and executive functioning.

Discussion

In this paper, we found widespread microstructural white matter aberrations in SZ participants, consistent with a large literature and with the view of schizophrenia as a disconnectivity syndrome, affecting distributed networks throughout the brain (Friston, 1998). We also found that there were three tracts in which greater white matter integrity in SZ patients was associated with a significantly better response to cognitive training, and these three tracts did not show white matter abnormalities at baseline. First, higher FA in SZ participants at baseline (prior to training) within the superior fronto-occipital fasciculus predicted significant training-induced improvement on attention/vigilance. The fronto-occipital fasciculus is the only long-range tract which provides direct connection between frontal and occipital areas (Catani and Thiebaut de Schotten, 2008; Lunven and Bartolomeo, 2016), and is critical for conveying visual information from occipital sensory cortices to the prefrontal cortex (Catani & Thiebaut de Schotten, 2008; Debrabant et al., 2016; Lunven &

Bartolomeo, 2016; Urbanski et al., 2008). It thus mediates visual attention processes, and damage to this tract has been associated with spatial neglect, consistent with the idea that attention to visual environmental stimuli depends on the coordinated activity of long-range connections between occipital and prefrontal cortical regions (Urbanski et al., 2008). Therefore, these findings are consistent with the present results showing that greater integrity of white matter within the fronto-occipital fasciculus is a good predictor of determining which patients show the most cognitive training induced gains in visual attention.

Second, greater FA integrity within the medial lemnisci and the corticospinal tracts (CST) predicted improved executive functioning after 70 hours of cognitive training. The medial lemniscus pathway contains pathways from the skin via the thalamus to the prefrontal cortex, and is therefore, vital for the analyses and integration of sensory-motor information. Lesions within this tract within the thalamus contribute to deficits in executive functions related to the planning, initiation, and regulation of goal-directed behavior (Carrera & Bogousslavsky, 2006; Van der Werf et al., 2003). The CST originates in frontal motor areas such the primary motor, premotor and supplementary motor cortices and terminates in the spinal cord, giving the CST a crucial role in movement planning and execution (Luppino & Rizzolatti, 2000; Rizzolatti, Luppino, & Matelli, 1998). It also must be noted that cortical afferents to frontal motor areas in the CST originate from three areas: the parietal lobe, the prefrontal cortex, and cingulate cortex, each of these areas are dedicated to a specific sensory-motor executive transformation. Thus, the CST mediates overall functioning of the cortical motor system (Luppino & Rizzolatti, 2000; Rizzolatti et al., 1998). Our data suggest that better baseline integrity within the tracts of the medial lemnisci and CST are associated with greater capacity to respond to training-induced analyses of sensory stimuli, sensorimotor integration and planning to drive better higher-order executive functioning in SZ patients after 70 hours of training.

Disruption of white-matter integrity is considered an integral component of schizophrenia. Our findings of widespread reduced FA in schizophrenia support Ellison-Wright's meta-analysis of diffusion tensor imaging (DTI) studies, showing anisotropy reductions in the myelin membranes in schizophrenia, which the authors posit results in a failure of overall sensorimotor integration and cognition (Ellison-Wright & Bullmore, 2009). Several studies across different techniques including two-photon laser microscopy, gene microarray analyses, DTI and magnetic transfer imaging, all provide converging evidence that disruptions in FA, particularly pertaining to prefrontal axon tract integrity, degrades axon myelination and impairs signal transduction and synaptic efficiency (Hakak et al., 2001; Segal et al., 2007; Chang et al., 2017), resulting in attention, working memory and executive functioning deficits in schizophrenia (Goldman-Rakic et al., 1997; Davis et al., 2003). Recent evidence from animal experiments has shown that by combining ex-vivo DTI with two-photon laser microscopy of intact mouse brains, white matter integrity as indexed by FA, is highly correlated with axon myelination (Chang et al., 2017). These findings suggest that FA is one index that may be a good indicator of myelin integrity, essential for propagating signal transmission for delivery of fast efficient and reliable functionally meaningful information between the environmental stimuli and the prefrontal cortex. Interestingly, in the present study, we demonstrate here that inter-individual variability in FA

within these long-range prefrontal-thalamic-sensorimotor connections in schizophrenia constrain the level of training-induced plasticity in systems that mediate improvement in both lower-level and higher-order cognitive operations. Specifically, SZ patients showed training-induced cognitive improvements mediated by intact white matter microstructure within long-range prefrontal tracts, in which patients with greater baseline FA manifested improved signal transmission and successful responsivity to cognitive training-induced modulation of learning plasticity and synaptic efficacy on attention and executive functioning measures. These findings indicate that patients who have increased FA levels to begin with, particularly in prefrontal tracts that show preserved white matter microstructure, are also more responsive and resilient to neural plasticity-based treatment interventions.

There are some limitations of the present study. These include methodological critiques of TBSS voxelwise analyses in which inferences can be made that greater FA may not always directly translate to greater white matter integrity. For example, TBSS voxelwise FA metrics are not sensitive to other factors that may affect tract integrity such as crossing fibers, which can contribute to water molecule mobility, influencing diffusion, and may explain the variation in white matter microstructure (Jbabdi et al., 2010). Such variation in white matter microstructure across regions may however still indicate that some tracts are more myelinated than others, and are maintained by increased metabolic activity, making them more likely to be a highly-connected hub to mediate communication within the brain network (Owen et al., 2015). This regional variation of white matter microstructure has been validated using edge density imaging and tractography, which takes into account the probability of crossing fibers while using streamlines to show tract-by-tract variation in streamline packing as a measure of connectivity between regions (Calamante, 2010; Calamante, 2011; Owen et al., 2015).

Although FA values are thought to represent the coherence of white matter as well as the microstructural properties of axons such as axon diameter, degree of myelination, and fiber packing density (Owen et al., 2013; Mukherjee et al., 2008), it is important to also examine other diffusion indices (such as mean, radial, and axial diffusivity) in schizophrenia in order to attain a more complete understanding of how microstructural integrity influences neural plasticity as a result of treatment interventions. Mean diffusivity (MD) is the diffusion rate averaged across all fiber orientations within a tract; axial diffusivity (AD) is the diffusion rate along fiber orientations of the axon, and radial diffusivity (RD) is the diffusion rate measured perpendicular to the fiber orientation. In disorders of white matter connectivity, such as schizophrenia, patients manifest decreased FA as well as elevated MD and RD, all of which are thought to contribute to reduced microstructural integrity (Kanaan et al., 2017; Seal et al., 2008). We did not find a correlation between any of the other diffusivity measures (mean, radial, axial diffusivity) with training-induced cognitive gains in schizophrenia, suggesting that these metrics did not uniquely predict cognitive gains, but rather may have contributed in a combinatorial manner to influence training-induced cognitive responsivity.

Finally, in order to increase power, we combined the behavioral analyses across the two training groups. Although we found no differences between the TCT vs. SCT groups in either baseline FA or behavioral change after 70 hours of training vs. baseline in the present study or in the larger clinical trial (Fisher et al., 2017), an increased sample size is needed to

examine the groups separately for future analyses to determine whether white matter coherence or training-induced effects are observed more in one group than the other group. We did not find any FA correlations with age in the schizophrenia patient group, consistent with some prior studies (Jones et al., 2006; Kanaan et al., 2017). We did not measure socioeconomic status or IQ status in HC participants; therefore, future studies are needed to ensure that these demographic measures are taken into account to minimize any confounding effects.

In conclusion, increased FA in prefrontal-thalamic-sensorimotor connections tracts may be useful as a future biomarker for predicting successful responsivity to cognitive training in patients with schizophrenia. These findings speak to the neural structural architecture that may underlie neural plasticity-based improvement and resilience in schizophrenia. Specifically, they suggest that although schizophrenia patients may have general myelination deficits in white matter microstructure, they may still be able to harness tracts that have intact myelin microstructure to optimize signal transmission as a compensatory or restorative mechanism to improve task performance.

Acknowledgments

Funding Source

This research was supported by the Brain and Behavior Research Foundation Young Investigator Award grant (NARSAD: 17680) and NIMH K01 grant (KO1MH82818) to Karuna Subramaniam, and the following NIH grants to Srikantan Nagarajan and Sophia Vinogradov (R01DC004855, R01DC010145, R21NS076171, R01MH068725 and R01DC013979). None of the authors have financial disclosures to declare. We thank Dr. Christine Hooker for her help with the set up of the MRI protocol, and Dr. Julia Owen who assisted with the DTI analyses.

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Figure 1.

Tracts showing significant reduction in FA in SZ patients ($N = 48$) compared with HC participants ($N = 28$), (regional reductions illustrated in blue voxels, TFCE, $p_{FWE} < 0.05$). Results are overlaid on the study-specific whole-group mean FA image and the whole-group mean FA skeleton.

Figure 2.

Front-occipital, corticospinal and medial lemniscus tracts illustrated in red, reveal tracts in which FA was not significantly different in SZ (N=48) vs. HC (N=28) participants, indicating relatively preserved white matter integrity within these tracts in SZ patients. Blue areas show tracts with reduced FA values in SZ vs. HC participants. Greater FA at baseline in right fronto-occipital tract is significantly associated with larger cognitive training-induced improvements in attention, and greater FA in right cortico-spinal tract and bilateral medial lemnisci is significantly associated with greater cognitive training-induced improvements in executive functioning in SZ patients who completed 70 hours of training

(N=30). Tracts were identified using the Johns Hopkins University Probabilistic Tractography and White Matter Labels Atlases (distributed with FSL).

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Table 1

Demographics (mean, SD) of Healthy Comparison (HC) and Schizophrenia (SZ) Participants

	HC (N=28)	SZ (N=48)
Age	41.41 (SD=11.74)	45.59 (SD=10.25)
Education	15.15 (SD=2.67)	13.34 (SD=1.58)
Gender	17M, 11F	33M, 15F

Table 2

Antipsychotic Medication and Clinical Symptoms, (mean, SD) in Schizophrenia (SZ) Participants

Antipsychotic Medication	SZ (N=48)
1st Generation (N)	7
2nd Generation (N)	43
Multiple (N)	7
No antipsychotic (N)	1
Other Psychiatric Medication	
Antidepressants or Mood Stabilizers (N)	30
Benzodiazepines (N)	9
Mean Chlorpromazine Equivalents	234.86 (189.55)
Mean Cogentin Equivalents	0.84 (1.36)
Illness Duration	24.52 (12.59)
Symptom Severity	
Overall Clinical Symptom Severity (PANSS)	64.26 (15.46)
Positive Symptom Severity (PANSS)	15.85 (5.22)
Negative Symptom Severity (PANSS)	15.81 (5.56)
General Psychopathology (PANSS)	32.60 (8.00)

Table 3

Targeted Cognitive Training Exercises

Auditory	Description	Visual	Description
High or Low	Sound sweep attention processing: Indicate the direction of two consecutive sound sweeps. Each one can sweep either up or down in pitch	Bird Safari	Identify the different bird from an array of birds presented peripherally. Presentation duration shortens as the task progresses to enhance attention and speed of processing capabilities
Match It	An auditory memory and executive function game: Match pairs of sound cards in a memory game	Jewel Diver	A multiple object tracking task testing attention, WM and executive function: Track moving target objects on the screen among distractors as they shift location
Tell Us Apart	A syllable attention and discrimination task: Select the syllable you just heard from a given pair. Syllables in the pair become increasingly similar as the difficulty increases	Master Gardener	A spatial WM and executive functioning task: Identify the two matching objects that rapidly appear on the screen in various spatial locations
Sound Replay	Memorize the syllables you just heard and click on them in the order you heard them. The sequence becomes longer as the task progresses, to enhance working memory (WM) and executive functioning capacities	Road Tour	A speeded attention/vigilance and executive functioning task: Correctly discriminate the vehicle in the center of the screen AND identify the road sign in the periphery.
Story Teller	Answer questions regarding facts and memorized details in a segmented story, intended to enhance memory and executive functioning	Sweep Seeker	An attention/vigilance and WM task in which the user is required to indicate the direction of two consecutive visual sweeps. Each one can sweep either inward or outward
Listen and Do	An auditory WM an executive functioning task: Listen to a sequence of verbal instructions and perform the required tasks. The number of instructions increases as the task progresses		

Table 4

Social Cognitive Training Exercises

Auditory	Description	Visual	Description
Prosody	A test of auditory emotion attention and discrimination: Correctly identify the prosody of the sentence with the neutral content	Face Match	A speeded face matching attention and discrimination task: Select the correct target face from an array of faces
Face Prosody	Emotional attention and executive function: Match the prosody of a target sentence to the correct facial expression	Gaze Match	A speeded gaze matching attention task (match gaze direction of target face)
Prosody Memory	Emotional WM and executive function: Match pairs of vocal emotion cards based on their prosody in a memory task	Mass Affect	Emotional identification, memory and executive functioning: Select the visual scene that generates the same affect as the target scene, over gradually longer periods of time
Emotional Story Telling	Answer questions regarding social interactions and facts in a segmented story: a test of higher-order emotional attention, memory and executive function	Name that Feeling	A speeded facial emotion identification task, using still images: correctly name the emotion displayed on the target face
		Second that Emotion	Match pairs of facial expression cards based on their emotion in a memory task

Table 5

Whole-brain group differences in FA values between HC and SZ participants at Baseline

Tract from TBSS masks	HC Mean FA	SZ Mean FA	p-value	Effect Size Cohen's d
Splenium of corpus callosum (SCC)	0.84058	0.8250	0.026	0.52
of corpus callosum Genu (GCC)	0.79401	0.7702	0.006	0.63
Cerebral peduncle right	0.7558	0.74259	0.020	0.57
Retrolenticular part of internal capsule right	0.65790	0.63758	0.019	0.57
Retrolenticular part of internal capsule left	0.71540	0.69068	0.006	0.70
Anterior corona radiata left	0.53604	0.519816	0.04	0.50
Posterior corona radiata right	0.56851	0.55268	0.020	0.56
Posterior corona radiata left	0.55381	0.54084	0.043	0.48
Sagittal stratum (include inferior longitudinal fasciculus and inferior-occipital fasciculus) left fronto	0.65311	0.63028	0.010	0.64
Posterior thalamic radiation (include optic radiation) right	0.71360	0.67945	0.00085	0.83
Posterior thalamic radiation (include optic radiation) left	0.68596	0.66296	0.013	0.62
Superior longitudinal fasciculus left	0.59631	0.58298	0.049	0.48