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

Karuna Subramaniam [a,*], Jeevit Gill [b], Melissa Fisher [c], Pratik Mukherjee [b], Srikantan Nagarajan [b], Sophia Vinogradov [c]

[a] Department of Psychiatry, University of California, San Francisco, San Francisco, CA, United States
[b] Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, United States
[c] Department of Psychiatry, University of Minnesota, MN, United States

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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 h (~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 h 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 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.



## 1. 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 and 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

* Corresponding author at: Department of Psychiatry, University of California, San Francisco, 513 Parnassus Avenue, HSE604, San Francisco, CA 94143, United States.
*E-mail address:* karuna.subramaniam@ucsf.edu (K. Subramaniam).

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(the medial portion of which includes the anterior thalamic radiation), with better integrity being associated with better working memory and executive functioning. Marenco 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 and MacDonald (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., 2017). 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 h 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 h 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.

## 2. Methods

### 2.1. 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 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, 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).

**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) | 45.59 (SD = 10.25) |
| Gender | 17M, 11F | 33M, 15F |

SZ subjects were stratified by age, education, gender, and symptom severity and randomly assigned to either: 1) 40 h of auditory processing exercises followed by 30 h of visual processing exercises (Targeted Cognitive Training Condition, TCT, N = 25); or, 2) 40 h of auditory processing exercises that included 10 h of training in auditory social cognition exercises, followed by 30 h of visual processing exercises that included 10 h 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 h 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 h of training.

### 2.2. 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

**Table 2**
Illness duration, antipsychotic medication and clinical symptoms, (mean, SD) in schizophrenia (SZ) participants.

| **SZ (N = 48)** | |
|---|---|
| Illness Duration | 24.52 (12.59) |
| **Antipsychotic Medication in SZ** | |
| 1st Generation (N) | 7 |
| 2nd Generation (N) | 43 |
| Multiple (N) | 7 |
| No antipsychotic (N) | 1 |
| Mean Chlorpromazine Equivalents | 234.86 (189.55) |
| Mean Cogentin Equivalents | 0.84 (1.36) |
| **Other Psychiatric Medication** | |
| Antidepressants or Mood Stabilizers (N) | 30 |
| Benzodiazepines (N) | 9 |
| **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) |

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