JUST STOP IT: THE ROLE OF VENTRAL ATTENTION NETWORK INTEGRITY ON REACTIVE INHIBITION IN SCHIZOPHRENIA

By

Livon Ghermezi

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ABSTRACT

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Cognitive control deficits are prevalent in schizophrenia patients (SZ). Previous research using reactive inhibition tasks has found SZ take longer to inhibit a prepared response. Abnormalities in the ventral attention network, which responds to unexpected stimuli, may play a role. The goal of this study was to examine whether structural integrity within this network is altered in SZ and relates to impaired reactive control over action in SZ. 20 SZ and 20 healthy controls (HC) performed an oculomotor variant on the stop-signal task and underwent diffusion tensor imaging. Subjects were required to make rapid eye movements to a target (T1) within an array. On some trials, the target jumped to a new location (T2), and participants were instructed to look directly at T2, inhibiting their saccade to T1. The time needed to inhibit (TSRT) was calculated. Probabilistic tractography was used to construct white matter tracts between primary visual cortex (V1), the ventral attention network (temporoparietal junction-TPJ and inferior frontal cortex-IFC), and supplementary eye fields (SEF). Microstructural integrity (FA) of these tracts was compared across groups and correlated with TSRT. Groups did not differ in speed of either STOP or GO latency. Increased positive symptoms and deceased occupational functioning predicted slower inhibition speeds in SZ. Additionally, SZ had decreased FA in V1-TPJ and IFC-SEF. Increased FA in TPJ-IFC significantly predicted decreased positive symptoms. FA of these three tracts did not predict the speed of inhibition. These findings suggest attention plays a role in inhibition tasks. However, the lack of correlations between tract integrity and performance makes it unclear whether these white matter differences are relevant to performance.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

Schizophrenia is an illness marked by cognitive dysfunction, such as cognitive control, attention, and information processing (Seymour et al., 2013; Sharif-Razi et al., 2013). Cognitive control refers to the process of choosing and monitoring thoughts and actions to achieve internal goals (Brass, et al., 2005). Due to the high prevalence of cognitive dysfunction in schizophrenia, several treatments have been focused on cognitive remediation and have shown positive results (see Mcgurk et al., 2007 for meta-analysis). Cognitive control deficits are specifically linked to functional outcomes in patients with schizophrenia, such as obtaining and maintaining an occupation (Karow et al., 2012; Schennach-Wolff et al., 2009; Sharif-Razi et al., 2013). It is important to understand the neurological underpinnings of cognitive control to be able to provide more targeted and useful combined treatments (ie. medications to be used in addition to cognitive remediation). One facet of cognitive control thought to be impaired in schizophrenia is response inhibition (Hughes et al., 2012; Kaladjian et al., 2011; Westerhausen et al., 2011; Zandbelt et al., 2011).

1.1 Response Inhibition in the Stop-Signal Task

Response inhibition is an executive motor function in which a routine or dominant response is intentionally stopped. Two strategies for implementing inhibition over action have been described: proactive and reactive inhibition (Braver, 2012; Kolodny et al., 2016; Lavallee et al., 2014; Schevernels et al., 2015; Vink et al., 2015). Proactive inhibition, sometimes referred to as action restraint, refers to the top-down attentional process of preparing an inhibitory response based on previous knowledge or expectations. On the other hand, reactive inhibition,

sometimes referred to as action cancellation, refers to the stimulus-triggered process of stopping a prepared response (Kolodny et al., 2016; Schevernels et al., 2015; Vink et al., 2015). Most researchers have focused solely on proactive inhibition when studying schizophrenia, but few have focused on reactive inhibition (Clementz, 1998; Gooding & Basso, 2008; Hutton & Ettinger, 2006; Westerhausen et al., 2011). However, given that these are two distinct processes that are mediated by at least partially distinct brain regions (Corbetta & Shulman, 2002) and show different responses to pharmacological interventions (Eagle et al., 2007, 2009; Favre et al., 2013), the reactive inhibition process is important in understanding and developing treatments for cognitive dysfunction in patients with schizophrenia. For this reason, we aim to increase understanding of reactive inhibition in schizophrenia to get a more well-rounded understanding of cognitive control dysfunction. For the remainder of this paper, reactive inhibition will be referred to simply as inhibition, as this is the facet of response inhibition that we will be further exploring.

One popular experimental paradigm developed to study inhibition is referred to as the stop-signal, or countermanding, task and requires the participant to make a response (i.e. push a button or make an eye movement) every time a go-signal is presented (i.e. visual cue). Occasionally, a stop-signal (i.e. auditory tone or visual cue) is presented at some short delay following the go-signal, and the participant must inhibit his/her response to the go-signal (Lappin & Eriksen, 1966). Performance on this task can be modeled by a GO process competing in a "race" with a STOP process. Depending on which process "won the race," the participant will either successfully inhibit his/her response, or fail to inhibit (Band et al., 2003; Camalier et al., 2007; Logan and Cowan, 1984). Difficulty is largely determined by the time between the go-signal and the stop-signal onset, referred to as the stop-signal delay (SSD). When SSD is longer,

the GO process has a greater head start in the race against the STOP process, making it less likely that the participant will be able to inhibit his/her response. The main measure of inhibition from this task, referred to as the stop-signal reaction time (SSRT), reflects the efficiency of inhibition—how long it takes for the participant to inhibit a response. It is calculated based on the distribution of GO RTs and the probability of failing to inhibit at particular SSDs.

Although SSRT is interpreted as a measure of inhibition, it is important to note that there are other factors that are involved in the task which also contribute to SSRT (Band et al., 2003; Boehler et al., 2012; Matzke et al., 2017; Salinas & Stanford, 2013). For the inhibitory (STOP) process to be triggered, the stop-signal must be both perceived (i.e. heard or seen) and interpreted as a signal that one should inhibit his/her response. Computational modeling work has emphasized the importance of efferent processing in the stop-signal task; a large chunk of SSRT comprises processing the STOP signal (Salinas & Stanford, 2013). Another noteworthy component is attention (Hampshire et al., 2010; Matzke et al., 2016; Salinas & Stanford, 2013; Vink et al., 2015). Attention is necessary to process the stop-signal and trigger the inhibition process to successfully perform in the task. The primary attentional network involved during the stop-signal task is the ventral attention network, which responds to unexpected or unattended to stimuli occurring outside the attentional focus (Corbetta & Shulman, 2002; Fox et al., 2006; Vossel, Geng, & Fink, 2014; Vossel et al., 2012). Calculations of SSRT do not take attention into account and researchers generally assume that longer SSRT means slowed inhibition, rather than difficulty maintaining attention, processing the STOP signal and triggering the inhibitory process.

1.2 Stop-Signal Task Neural Findings in Healthy Individuals

Much of the current research on the neural basis of performance on the stop-signal task (and its variants) on healthy individuals has been conducted using functional MRI (fMRI). Many of these researchers have found that the right inferior frontal cortex (IFC) shows greater activation on stop trials compared to go trials (Aron & Poldrack, 2006; Hughes et al., 2012; Lavallee et al., 2014; Matzke et al., 2016; Vink et al., 2015), and it has been suggested to have a direct role in motor inhibition. Several researchers have challenged this explanation with their findings that IFC is also activated during a stop-signal task condition in which participants are instructed to ignore a particular signal (Hampshire et al., 2010; Sharp et al., 2010). Thus, these groups have argued that the IFC is activated when important cues are detected, such as the stop-signal, and is not related to response inhibition per se. Their findings suggest that the IFC activation that researchers have been finding is not due to inhibitory processes, but attentional processes. This is a likely hypothesis since the IFC is a key node in the ventral attention network. The ventral attention network is comprised of the temporoparietal junction (TPJ) and ventral frontal cortex (VFC) – which includes the IFC and middle frontal gyrus (MFg), and is involved in stimulus-driven allocation of attention (Corbetta & Shulman, 2002). More specifically, the ventral attention network is a bottom-up process that generally responds when task-relevant stimuli occur unexpectedly, or outside the area of focus (Corbetta & Shulman, 2002; Vossel, Geng, & Fink, 2014). Researchers who have highlighted the IFC as a region involved in directing attention to unexpected events (ie. stop-signal) have also emphasized the role of areas such as pre-supplementary motor area (pre-SMA) in receiving information from the IFC and inhibiting the motor responses (Hampshire et al., 2010; King et al., 2012; Sharp et al., 2010). The preSMA is part of the supplementary motor cortex (SMC) and is heaviliy implicated in more

complex aspects of movement control. For example, it is suggested that pre-SMA is responsible for intentional locomotion and is invovled in inhibiting those actions as well (Hsu et al., 2011; Hu & Li, 2012; Nachev et al., 2007; Sharp et al., 2010; Swick, Ashley, & Turken, 2011). The supplementary eye field (SEF) is the oculomotor homologue of pre-SMA, and has been shown to be involved in controlling and inhibiting planned eye movements (Schall and Boucher, 2007; Sharika et al., 2013).

A handful of studies have also examined the relationship between brain structure and reactive inhibition. Diffusion tensor imaging (DTI) is a magnetic resonance technique that uses the diffusion of water through brain tissue to estimate the orientation, location and integrity of white matter fiber structures. DTI data yields a well-established index of white matter tract integrity called fractional anisotropy (FA). FA describes the degree of structural integrity within a specific voxel. Values range from 0 (completely isotropic, with no restriction in direction of diffusion) to 1 (completely anisotropic, with diffusion occurring strictly in one direction). These values are influenced by fiber density, axonal diameter, myelination, and fiber coherence, and a higher value indicates that information can pass more quickly and efficiently between nodes (Alexander et al., 2007; Pierpaoli & Basser, 1996). If a given white matter pathway is important to task performance, then higher FA in that pathway should yield faster reaction times. One DTI study on typically developing children found that higher FA values in the IFC and pre-SMA correlated with faster response inhibition (Madsen et al., 2010). Another study on healthy adults found similar results with higher FA values in a tract connecting SEF and IFC being related to faster SSRTs (Thakkar et al., 2016).

1.3 Research Findings in Patients with Schizophrenia

Compared to healthy individuals, patients with schizophrenia tend to show slower SSRTs using both hand (Bellgrove et al., 2006; Enticott, Ogloff, & Bradshaw, 2008; Fortgang, Hultman, van Erp, & Cannon, 2016; Hughes et al., 2012) and eye (Thakkar et al., 2011, 2015) responses. Additionally, longer SSRT has been related to poorer occupational functioning and more negative symptoms (Bellgrove et al., 2006; Thakkar et al., 2011; Thakkar et al., 2015). Others have found that patients with schizophrenia did not necessarily show prolonged SSRT, but observed data suggesting that patients have a difficulty with triggering the inhibitory response, which may be due to difficulties processing or attending to the stop-signal (Badcock et al., 2002; Matzke et al., 2016). In fMRI studies, patients with schizophrenia showed reduced activation in the IFC during stop signal trials (Chen, Bidwell, & Holzman, 2005; Hughes et al., 2012). Reduced IFC activation may relate more to attentional difficulties than inhibition processes, but current results cannot disambiguate these two hypotheses.

1.4 Current Study

In the current study, we used an oculomotor variant of the stop-signal task called the search-step task. The search-step task, unlike the stop-signal task, requires the participant to not only cancel an action, but to change that action – in this case, a saccadic eye movement. It is still possible to calculate the speed of inhibition, called target step reaction time (TSRT), in an analogous manner to SSRT (Camalier et al., 2007). In this version of the task, visual stimuli were used for both go and stop signals to decrease multimodal processing, providing an advantage over the typical stop-signal task. Studies have shown that patients with schizophrenia

have difficulty processing multiple cues at once, especially when they are in different modes – ie. visual and auditory (Granholm et al., 1996; Kim et al., 2004; Nuechterlein et al., 2006). In addition, we used eye movement responses rather than button presses. This has major advantages because unlike hand movements (button presses), basic saccadic eye movements are intact in patients with schizophrenia (Mahlberg et al., 2001) making it easier to interpret impaired inhibition task performance (Thakkar et al., 2015).

We used DTI data to investigate the structural integrity of white matter tracts involved in reactive inhibition. Specifically, we examined three tracts: the neural pathway connecting the early visual cortex (V1) and temporoparietal junction (TPJ; a node in the ventral attention network), TPJ to IFC (the ventral attention network), and IFC to SEF, which arguably has a more direct role in inhibition. DTI can provide us to with an index of the structural integrity specific neural pathways, thus allowing us a proxy measure of how efficiently information can pass from one region to the other. This is the first study to our knowledge that utilizes DTI data to investigate potential neural mechanisms of reactive inhibition impairments in patients with schizophrenia. Our predictions were as follows. First, based on previous work, we hypothesized that inhibition efficiency during the search step task, indexed using TSRT, would be slower in patients diagnosed with schizophrenia, compared to healthy individuals. Second, we hypothesized that the structural integrity (FA) of the three tracts will be reduced in individuals diagnosed with schizophrenia compared to healthy individuals. Third, we hypothesized that, consistent with prior findings (Thakkar et al., 2016), FA in the pathway between IFC and SEF will predict inhibition task performance in both groups, such that increased FA will be associated with faster inhibition speed. Finally, we hypothesized that these behavioral and DTI measures would have clinical relevance. Namely, we predicted positive correlations between TSRT and

clinical symptoms and occupational functioning, consistent with prior findings (Thakkar et al., 2011, 2015). In addition, we explored the relationship between tract FA and both symptom severity and occupational functioning.

2. METHOD

2.1 Participants

Twenty individuals who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia or schizoaffective disorder (SZ) were recruited from the Genetic Risk and Outcome in Psychosis study (Kahn et al., 2011) and from treatment-seeking patients at a hospital in The Netherlands. Twenty healthy individuals (HC) with no personal or family history of psychiatric or neurological illness were recruited through community advertisements. Diagnosis of the SZ group was determined by clinicians using the Comprehensive Assessment of Symptoms and History interview (Andreasen and Flaum, 1992) or Schedules for Clinical Assessment for Neuropsychiatry version 2.1 (Wing et al., 1990). Clinical symptoms were assessed in patients using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Scores were converted into qualitative descriptive labels (see Table 1 for category labels). Occupational functioning was assessed using the Social Functioning Scale (SFS; Birchwood et al., 1990). All participants had normal or corrected to normal vision. Participants were excluded if there was a history of significant head trauma, neurological illness, or substance abuse or dependance within 6 months before the study. The SZ and HC subjects were matched for age, gender, IQ, and handedness; demographic data are presented in Table 1.

2.2 Saccadic Search Step Task

The task used in this study is an oculomotor variation of the stop-signal task and was performed in an MRI scanner (Figure 1). Following a variable 1000 – 2000 ms fixation period, one of three randomly interleaved trial types were presented for 4 s: no-step (30% of trials), redirect (40% of trials), and follow (30% of trials; control condition). Each trial consisted of an eight-element search array, where each element subtended 0.7° visual angle and were isoluminant and equidistant from the center (9° visual angle). On no-step and redirect trials, after the fixation period, the search array was presented with one red singlton among green distractors. On no-step trials, this array remained on the screen for the entire 4 s. On redirect trials, however, the red target jumped to a new location on the array following a short delay after the initial presentation (target step delay; TSD). On no-step and redirect trials, participants were instructed to saccade to the red target (T1) as quickly as possible. They were instructed that if the target jumped to a new location (redirect trials), they should try to inhibit the saccade to T1 and look as quickly as possible to the targets new location (T2). On follow trials, the eight-element array appeared with two red targets among green distractors, and remained on the screen for the entire 4 s. On these trials, participants were instructed to look at each red target in succession (the order was not important). Redirect trials in which the participant successfully looked directly at T2 and inhibited the T1 response were referred to as compensated trials. Redirect trials in which the participant erroneously looked at T1 first were referred to as noncompensated trials. As TSD increases, it becomes more difficult to inhibit the saccade to T1 (Camalier et al., 2007; Logan and Cowan, 1984). The TSDs were dynamically adjusted throughout the task to ensure an approximately 50% rate of compensated and noncompensated trials on the redirect trials. Initial TSD was set to 100 ms and increased or decreased by 67 ms when the participant succeeded or

failed to inhibit, respectfully. To minimize the chance of a saccade landing midway between T1 and T2 on redirect and follow trials, target locations were set at least 90° apart.

Trials were presented in four blocks of 60 trials, each lasting five minutes. In total, 72 no-step trials, 72 follow trials, and 96 redirect trials were presented. Participants were trained on the three trial types before imaging data aqcuisition. Participants were instructed to respond both as quickly and as accurately as they could, but were also told that inhibition of the saccade to T1 on redirect trials would not always be possible. Participants were not explicitly told how likely each trial type was to occur.

2.3 Stimulus Display and Eye Tracking

Task stimuli were displayed on an MR compatible LED screen using Presentation software (Neurobehavioral Systems). The screen was placed at the rear of the bore of the scanner and was viewed by the participant via a mirror on the head coil. Eye movements were recorded during scanning using an MR compatible infrared camera (Nordic Neuro Lab, Bergen, Norway). Eye position was sampled at a rate of 60 Hz. Acquisition was controlled by ViewPoint eyetracking software (Arrington Research). Accuracy of redirect trials was determined online to determine TSD on the subsequent step trial.

2.4 Analysis of Eye Movement Data

Eye position data were analyzed offline using a semiautomated MATLAB procedure (The MathWorks). Eye position data was differentiated to obtain a velocity signal and then

filtered with a fifth-order Butterworth filter (40 Hz cutoff). Then, saccade onsets were determined automatically using liberal velocity criteria. After this automated procedure, erroneously marked saccades (e.g., camera noise, head movements, blinks, etc.) were removed manually.

Trials in which saccades were produced less than 100 ms following array onset were considered anticipatory and excluded from further analysis. Saccade accuracy was also determined using an automated procedure. On redirect trials, trials were classified as compensated if the saccade landed closer to T2 than T1 and as noncompensated if the saccade landed closer to T1 than T2. The speed of saccade execution (the GO process) can be observed directly from RT on no-step trials, which was calculated as the time between array onset and saccade onset. The speed of saccade inhibition (the covert STOP process) can be inferred according to the horse-race model. Following from this race model logic, the time needed to respond to the target step and cancel the planned saccade to T1 (target step reaction time, TSRT) can be estimated. TSRT was calculated using the integration method (Verbruggen et al., 2013) by sorting no-step RTs and finding the RT corresponding to the proportion of noncompensated trials. Then the mean TSD was subtracted from this RT (Figure 2). This is a measure analogous to SSRT that is calculated from the stop-signal task.

2.5 Image Acquisition

All MRI data were acquired at the University Medical Center Utrecht on a Philips Achieva 3T scanner (Philips Medical Systems, Best, The Netherlands) equipped with an eight-channel head coil allowing parallel imaging. Two diffusion images were acquired using single-

shot echoplanar imaging sequences, consisting of 30 diffusion-weighted scans (b=1000 s/mm^2) with noncollinear gradient directions and one image without diffusion weighting, b=0s/ mm2), covering the entire brain (Repetition Time (TR) = 7,057 ms; Echo Time (TE) = 68 ms; field of view = 240 mm × 240 mm × 150 mm; in plane resolution = 1.875 mm × 1.875 mm; slice thickness = 2 mm; no slice gap; 75 axial slices; matrix size 128 mm × 99 mm). The diffusion weighted scans were measured twice, once with phase encoding direction reversed (first scan posterior–anterior, second scan anterior–posterior), in order to correct for susceptibility induced spatial distortions (Andersson and Skare, 2002). For registration purposes, a whole-brain three-dimensional T1-weighted scan (200 slices; TR = 10 ms; TE = 4.6 ms; flip angle = 8°; field of view, 240 mm × 240 mm × 160 mm; voxel size: 0.75 mm × 0.8mm × 0.75 mm) was acquired.

2.6 Data Analysis

2.6.1 Regions of Interest

We examined connectivity between nodes in the ventral attention network as well as regions more directly involved in movement inhibition. The ventral attention network comprises the IFC and TPJ and responds to incoming visual stimuli via the primary visual cortex (V1). Thus, we looked at connections between V1 - TPJ and between TPJ - IFC. Additionally, to look at the regions necessary for adjusting the pre-programed eye movements (GO response), connections between SEF, which is more directly involved in eye movement control, and IFC were examined. Since previous research using the stop-signal taks (and its variants) found increased activation of IFC in the right hemisphere only, all regions of interest (ROIs) were confined to the right hemisphere (Hampshire et al., 2010; Hughes et al., 2012; Lavallee et al.,

2014). In order to define the ROIs, we used functional imaging data that was obtained while subjects performed the search-step task (see Thakkar, et al., 2014 for more detailed description of fMRI data analysis). More specifically, we examined activation that was greater for compensated than no-step trials to define IFC, TPJ, and SEF. To define V1, we examined activation that was greater for no-step trials than fixation. Functional data from both groups (SZ and HC) was averaged in standard (Montreal neuroimaging; MNI) space, and the center of each ROI was defined by identifying the voxel in each broadly defined region (V1, TPJ, IFC, SEF) that was most activated on compensated vs. no-step trials (for IFC, TPJ, and SEF), or no-step trials vs. fixation (for V1) on the group level. Once the center of the ROI was defined, we created a 10mm sphere around that voxel to define the entire ROI. This way, we used the same ROI location for each participant, regardless of group association.

2.6.2 Preprocessing

The diffusion-weighted scans were preprocessed and analyzed using FSL 5.0. As DTI scans suffer from spatial distortions along the phase encoding direction, two diffusion-weighted scans were acquired with reversed phase encoding blips, resulting in pairs of images with distortions going in opposite directions. From these two images, the off-resonance field was estimated. Next, the 30 diffusion-weighted images from each phase-encoding direction were realigned to the b0 image using affine registration, and eddy current correction was applied. The eddy-corrected scans with opposite phase encoding blips were then combined into a single corrected image using the previously estimated off-resonance field. A brain mask was created for the mean b0 image and applied to all diffusion-weighted images.

DTI analyses must be performed in native space as diffusion gradients are specified in this space; however, ROIs were created in standard (MNI) space. To transform the ROIs into each participant's native space, the anatomical T1-weighted volume was realigned to the mean b0-weighted image and then normalized to MNI-space using the unified segmentation algorithm as implemented in SPM8 (Ashburner and Friston, 2005).

2.6.3 Probablistic Tractography

We were interested in three tracts in this study, V1-TPJ, TPJ-IFC, and IFC-SEF. Probabilistic tractography is a method in which the fiber tract that most likely connects two brain regions is estimated based on the direction of diffusion (Beaulieu, 2002). To do this, 10,000 streamlines were sent out from each voxel within a node, and given an end point (ie. if V1 is the start point, TPJ would be set as the end point). Only streamlines which start at the seed (start point) and end at the target (end point) were included in the tract. All probablistic tractography analyses used each ROI as both a seed and a target, such that streamlines were sent out in both directions. Additionally, we used a mask of the saggital midline so that tracts did not cross over into the left hemisphere. The probabilistic tractography resulted in a value for each voxel equal to the number of streamlines that passed through that particular voxel. Next, we masked out any gray matter and only used white matter for further analyses. This is because gray matter has relatively low FA and presents more diffuse tracks than in white matter, making it more difficult to analyze (Hagler et al., 2009). In each participant, each probabilistic white matter tract in native space was then normalized into MNI space and averaged across participants in each group. Tracts for each group were created by including only the top 0.27% (3σ above mean in normal distribution) of voxels with the highest values (i.e. most streamlines passing through).

Those thresholded group tracts were then binarized. Since diffusion imaging cannot differentiate between forward and backward projections, we used the overlap of both directions to define the most probable track. FA values were extracted and averaged across voxels within each tract for each subject.

2.6.4 Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics 23.0. First, mean GO latency (no-step RT) and STOP latency (TSRT) were calculated for each participant. We then conducted two independent samples t-tests to compare average STOP and GO latencies between the two groups. In order to determine if STOP latency is related to clinical symptoms and occupational functioning in patients, we performed a number of linear regression analyses, with PANSS positive, PANSS negative and SFS occupational functioning subscale scores as independent variables and TSRT as the dependent variable. Next, we assessed if there were overall group differences in the microstructural integrity of the three tracts (V1 - TPJ, TPJ - IFC, IFC - SEF). We computed mean FA values for each subject within each binarized tract. Separate independent samples t-tests were used to compare the FA values in the three tracts across groups. To test whether tract microstructural integrity predicted the speed of the latent STOP process, we performed three multiple regression analyses, for each of the three tracts using grand mean centered FA, group, and the interaction between FA and group as independent variables and the STOP latency as the dependent variable. To test if microstructural integrity in each tract was correlated with patient clinical symptoms and occupational functioning, we performed seperate linear regression analyses with FA in each tract as the independent variable, and PANSS positive, PANSS negative and SFS occupational functioning subscale score as the dependent

variable. Finally, we performed Spearman correlations to assess if medication equivalence dose (CPZ dose) was correlated with FA in each of the three tracts, STOP latency, and GO latency.

3. RESULTS

3.1 Behavior

Mean GO latency (no-step RTs) was 325 ms (SD = 80 ms) for controls and 311 ms (SD = 63 ms) for schizophrenia (Figure 3). The mean STOP latency (TSRT) was 159 ms (SD = 17 ms) for controls and 171 ms (SD = 28 ms) for schizophrenia. An independent samples t-test was computed to test whether schizophrenia patients differed from controls in STOP and GO latencies. There was no significant difference in STOP and GO latencies between groups ($t(38) = -1.59$, $p = 0.12$, $d = 0.52$; and $t(38) = 0.63$, $p = 0.53$, $d = 0.20$, respectively). GO and STOP latencies were not correlated ($r(38) = 0.18$, $p = 0.28$).

Several linear regressions were run in order to determine if STOP latency was linked to clinical symptoms and occupational functioning in patients (Table 2). Positive symptoms of schizophrenia accounted for 24.1 percent of the variance in STOP latency ($F(1,18) = 5.09$, $p = 0.038$, $R^2 = 0.24$), while negative symptoms did not account for variance in STOP latency ($F(1,18) = 0.198$, $p = 0.662$, $R^2 = 0.01$). Increased positive symptoms was linked to slower inhibition speed in patients. Additionally, occupational functioning accounted for 28.7 percent of the variance in STOP latency ($F(1,18) = 6.44$, $p = 0.022$, $R^2 = 0.29$); better occupational functioning was associated with faster inhibition speed. Finally, correlations were run to see if medication dose was correlated with the speed of the latent STOP and GO processes. We found

that CPZ dose was not correlated with either STOP or GO processes ($p = 0.46$ and $p = 0.67$, respectively).

Based on previous findings from the double-step task, we expected TSRT to be longer in SZ (Thakkar et al., 2015). As a post-hoc explanation for the null results, we considered that patient symptom severity was greater in the previous sample than the current sample. Leucht et al. (2005) found that PANSS total scores of 58 corresponded to Clinical Global Impressions (CGI) ratings of being considered "mildly ill," PANSS total scores of 75 corresponded to being considered "moderately ill," PANSS total scores of 95 being concidered "markedly ill," and PANSS total scores of 116 concidered "severely ill." Our patient sample had an average PANSS total score of 52.89 (SD = 17.71), suggesting our patients fell in the "mildly ill" to "moderately ill" range. Further, to assess whether the patient samples between the current study and Thakkar et al. (2015) study differed, we first had to convert our PANSS positive and negative subscale scores to Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) scores, respectively. When we converted our PANSS positive and negative subscale scores to SAPS and SANS scores, respectively (using formulas provided in Van Erp et al., 2014), we had an average estimated SAPS score of 14.91 (SD = 12.69) and average estimated SANS score of 20.68 (SD = 13.86). The patient sample in Thakkar et al. (2015) had an average SAPS score of 17.0 (SD = 7.8), and average SANS score of 24.8 (SD = 14.4). We ran two 2-sample t-tests to compare the mean scores and standard deviations of SAPS and SANS between studies. We found that our patient sample did not significantly differ from the Thakkar et al.'s (2015) patient sample in symptom severity ($t(32) = 0.57$, $p = 0.57$; and $t(32) = 0.85$, $p = 0.40$, respectively). Therefore, although our sample was a relatively high functioning

group of patients (as suggested by PANSS total scores falling in the mild to moderately impared range), we cannot conclude that symptom severity wholly accounts for our null finding.

3.2 DTI

One healthy control and one schisophrenia patient did not complete a DTI scan, and a second schizophrenia patient was excluded from the DTI analyses due to poor quality of the DTI scan. Analyses were conducted on the remaining 19 HC and 18 SZ. The three spatially normalized, group-averaged, and statistically thresholded probabilistic tracts (V1-TPJ, TPJ-IFC, and IFC-SEF) are shown in Figure 4. Three independent samples t-tests were used to test whether the microstructural integrity of the three tracts differed between the two groups (Figure 5). Patients had significantly lower FA than controls in the tracts between both V1-TPJ and IFC-SEF ($t(35) = 16.01$, $p < 0.001$, $d = 5.27$; and $t(35) = 2.86$, $p = 0.007$, $d = 0.94$ respectively). FA in the tract connecting TPJ-IFC was not significantly different between groups, however, patients did have higher FA in this tract at trend level ($t(35) = -1.86$, $p = 0.07$, $d = -0.61$). Several multiple regression analyses were run to test if group and microstructural integrity in each tract predicted the speed of the latent STOP process. We included the interaction between group and FA in each tract in the regression analysis to examine whether the effect of FA on TSRT differed depending on group. Prior to computing the regression, FA in each tract was centered around their means, and the interaction effect was computed by multiplying the mean-deviated FA by group. The regression results for V1-TPJ, TPJ-IFC, and IFC-SEF are presented in tables 6, 7, and 8, respectively. None of the regression models were significant, suggesting that FA in each tract, group, and their interactions did not predict the speed of the latent STOP process ($F(3,33) = 1.03$,

p = 0.39; F(3, 33) = 1.67, p = 0.19; F(3, 33) = 1.91, p = 0.15 for V1-TPJ, TPJ-IFC, and IFC-SEF, respectively, with mean-deviated FA, group, and the interaction).

We performed regression analyses to assess the extent to which microstructural integrity in each tract predicted positive symptoms (Table 3), negative symptoms (Table 4) and occupational outcomes (Table 5) in patients with schizophrenia. Higher FA in TPJ-IFC significantly predicted decreased positive symptoms in patients ($F(1, 16) = 8.45$, $p = 0.010$, $R^2 = 0.35$). Regression results showed a trend-level effect of FA in IFC-SEF on positive symptoms in the expected direction (increased FA associated with decreased symptoms; $F(1,16) = 3.35$, $p = 0.086$). Additionally, results showed a trend-level effect of FA in TPJ-IFC and IFC-SEF on occupational functioning in the expected direction (increased FA associated with increased functioning; $F(1,16) = 3.61$, $p = 0.075$; and $F(1,16) = 3.20$, $p = 0.092$, respectively). All other regression analyses revealed non-significant associations between FA and positive symptoms, negative symptoms, and occupational functioning (all p-values > 0.3). To see if medication dose was correlated with FA in each tract, we conducted Spearman correlations, and found no significant correlations between CPZ dose and FA (all p-values > 0.4).

4. DISCUSSION

In this study, individual and group differences in the speed of saccade execution and inhibition were investigated in individuals diagnosed with schizophrenia and demographically matched healthy controls with respect to structural integrity of connections within a right-lateralized network of regions of the ventral attention network (TPJ, IFC), early visual cortex

(V1), and a higher oculomotor region (SEF). Groups did not differ in speed of either STOP or GO latency; however, increased positive symptoms and decreased occupational functioning predicted slower STOP latency in individuals diagnosed with schizophrenia. Additionally, we found that individuals diagnosed with schizophrenia had significantly lower FA in V1-TPJ and IFC-SEF, and higher FA at a trend in TPJ-IFC when compared to healthy individuals. Tract FA in each of the three tracts, group, and the interaction between FA and group did not predict TSRT. When assessing clinical relevance, we found that higher FA in TPJ-IFC significantly predicted decreased positive symptoms in patients with schizophrenia. Higher FA in IFC-SEF predicted decreased positive symptoms, and increased occupational functioning at a trend. Finally, increased FA in TPJ-IFC predicted increased occupational functioning at a trend.

Given previous findings that SZ take longer to inhibit their responses than HC (Thakkar et al., 2015), we expected to find a group difference in TSRT in the current study. However, although the effect size was in the medium range (d = 0.52), TSRT was not significantly longer in patients. One pausible explanation is that because our patient sample was relatively high functioning, there was reduced variance in performance, thus making it less likely to find a significant link. Another potential reason we did not find group differences in TSRT may be due to study design. Given that unimodal processing and saccadic responses are relaitvely intact in SZ, and the current study used both, it is possible that group differences in inhibition reaction time are more subtle and difficult to detect. One way to assess this is by conducting a follow-up study and running participants in both variants of the stop-signal task ("traditional" task where the stop-signal is an auditory cue and the current unimodal/saccadic variation of the task).

Patients had significantly lower FA than controls in the tracts between both V1-TPJ and IFC-SEF. V1 is involved in early visual processing, while TPJ is a node in the ventral attention

network, which is associated with target detection of stimuli based on salience (Corbetta & Shulman, 2002). The tract between V1-TPJ is likely how incoming visual stimuli is assessed for salience, so lowered FA in V1-TPJ may suggest that individuals with schizophrenia have less efficient allocation of attention to salient visual cues than healthy individuals. Supporting this notion, Jimenez et al. (2016) found that individuals diagnosed with schizophrenia had both increased deactivation of TPJ in lower cognitive load trials of a target detection task during functional MRI, as well as failure to deactivate TPJ in higher cognitive load trials. These results suggest that patients with schizophrenia may have difficulty orienting attention specifically to salient cues and have difficulty distinguishing targets from non-targets. Thus, reduced FA of V1-TPJ, suggesting increased diffusivity, may result in less incoming information from V1 to the ventral attention stream, making it more difficult for individuals diagnosed with schizophrenia to orient attention to salient cues. Additionally, we examined the tract between IFC – SEF. IFC is a node in the ventral attention network associated with target detection of salient stimuli (Aron, Robbins, & Poldrack, 2004), while SEF has been associated with executive control over eye movements (Stuphorn, Taylor, & Schall, 2000). Thus, lowered FA in the tract connecting these two regions may suggest that patients take longer to inhibit saccadic eye movements based on stimulus salience than healthy controls.

When assessing if FA in our three tracts predicted clinical symptoms and occupational functioning, we found increased FA in TPJ-IFC significantly predicted decreased positive symptoms in patients. This finding suggests that individuals with greater structural integrity of the ventral attention network also had decreased positive symptoms. This relationship between ventral attention network structure and positve symptoms is consistent with the literature showing that increased attention to irrelevant stimuli is correlated with more positive symptoms

(Galaverna, Morra, & Bueno, 2012; Morris et al., 2013). It is likely that an inability to maintain attention to only relevant stimuli is due to less intact attention networks. However, this conclusion is complicated by the fact that we did not find any group differences in FA of TPJ-IFC. No other tracts predicted positive symptoms, negative symptoms or occupational functioning.

The nodes in our study are also part of the superior longitudinal fasciculus (SLF). The SLF is a white matter fiber tract that connects the frontal, occipital, parietal and temporal lobes, and consists of four separate components, each of which has a different function. Notably, SLF I is likely involved with regulating motor behavior, while SLF II is likely involved with controlling spatial attention, as well as visual and oculomotor functions, and SLF III is likely invoved in transfering somatosensory information to premotor areas. The fourth component is more involved with auditory and language processes (Kamali et al., 2014; Makris et al., 2005). Notably, SLF I, II and III includes at least parts of the three tracts included in this study (V1-TPJ, TPJ-IFC, and IFC-SEF). The findings of FA within SLF in individuals diagnosed with schizophrenia are mixed. One study found that FA in SLF I (the component of SLF which includes the tract between V1 and TPJ) was significantly higher in patients diagnosed with schizophrenia when compared to healthy individuals (Wu et al., 2015). However, other studies found decreased FA in schizophrenia patients across components of SLF (Guo et al., 2012; Karlsgodt et al., 2008). Given that our sample size was relatively small, we might have been underpowered to detect behavioral and FA differences between groups. Thus, it could be that with a larger and more diverse sample, this link between IFC-SEF and STOP latency would be significant.

In trying to understand the neurobiological correlates of reduced FA, it is important to keep in mind the several factors that can influence it, including fiber density, axonal diameter, axonal damage, myelination, and fiber coherence. Further, DTI does not include information about the direction of the connections. Thus, it is not possible to conclude the direction in which FA is decreased in patients (ie. V1 to TPJ, or vice versa?).

The findings of the current study should be interpreted in light of several limitations. First, our patient population was relatively high functioning and likely not representative. Recruiting a more representative sample can be challenging because individuals with lower levels of functioning often have difficulties with transportation, and disorganization which impedes their ability to travel to/from appointments, and keep track of appointment times. This lack of a representative sample may account for the similarities between groups in STOP and GO latencies. Additionally, all patients in the current study were on antipsychotic medications, which may make group differences difficult to interpret. To assess this, we ran exploratory correlations with medication equivalence doses (CPZ dose), FA, GO RT, and STOP RT. We found that CPZ dose was not correlated with FA, STOP, or GO latency, suggesting that medication cannot completely account for our findings. Despite the small sample size and high functioning patient group, however, we were still able to find significant group differences in FA in two of the tracts, as well as significantly predict positive symptoms and predict STOP latency at a trend.

In conclusion, groups did not differ in speed of either STOP or GO latency. Increased positive symptoms and decreased occupational functioning predicted slower inhibition speeds in patients with schizophrenia. We found significant decreases in FA in V1-TPJ and IFC-SEF, with marginally increased FA in TPJ - IFC in SZ, compared to HC. White matter tract integrity of these three tracts did not predict the speed of inhibition in either group, and medication dose did

not predict task performance in SZ. Finally, we found that increased FA in TPJ – IFC significantly predicted decreased positive symptoms in SZ. Additionally, increased FA in IFC-SEF predicted marginally decreased positive symptoms and marginally increased occupational functioning in SZ, while increased tract integrity of TPJ – IFC predicted increased occupational functioning at a trend. The findings in the present study suggest that inhibition efficiency has clinical correlates in individuals diagnosed with schizophrenia. Additionally, white matter pathways in a network of regions involved in processing stimulus salience and using that information to guide action are disrupted in patients with schizophrenia. Given that the pathways examined in this study are a part of the SLF - a bundle of white matter fibers involved in attention and motor processes, it is likely that attention plays a role in inhibition tasks. However, given the lack of correlations between tract integrity and performance, it is unclear whether these white matter differences are relevant to inhibition task performance.

APPENDICES

APPENDIX A: Tables

Table 1.

Demographics

	HC (n=20)	SZ (n=20)	HC vs SZ	
			Statistic	p
Age	34.7 (8.9)	36.9 (8.2)	t = 0.81	0.42
Sex	8 M/12 F	6 M/14 F	χ^2 = 0.83	0.36
Handedness[a]	0.8 (0.4)	0.9 (0.2)	t = 0.99	0.33
IQ	102.3 (12.6)	95.3 (12.0)	t = 1.65	0.11
Education[b]	6.8 (1.7)	4.8 (1.7)	t = 3.65	<0.001
SFS Employment	--	107.7 (10.3)	--	--
PANSS Positive	--	12.2 (5.2)	--	--
PANSS Negative	--	13.4 (6.4)	--	--
PANSS Total[c]	--	52.9 (17.7)	--	--
Illness Duration (years)	--	14.4 (5.2)	--	--
CPZ Equivalent (mg)	--	280.0 (273.4)	--	--

Abbreviations: SFS Employment, Occupational Functioning score for Social Functioning Scale; PANSS Positive, Positive Symptom score for Positive and Negative Syndrome Scale; PANSS Negaative, Negative Symptom score for Positive and Negative Syndrome Scale; CPZ Equivalent, Chlorpromazine equivalent antipsychotic dose.

Note: [a]Handedness based on the Edinburgh Handedness Inventory; scores range from 0 indicating complete left-handedness to 1 indicating complete right-handedness.

[b]Education based on categories: 0 = <6 years of primary education; 1 = finished 6 years of primary education; 2 = 6 years of primary education and low-level secondary education; 3 = 4 years of low-level secondary education; 4 = 4 years of average-level secondary education; 5 = 5 years of average-level secondary education; 6 = 4 years of secondary vocational training; 7 = 4 years of high-level professional education; 8 = university degree.

[c]PANSS Total categories: 58 = mildly ill; 75 = moderately ill; 95 = markedly ill; 116 = severely ill.

Table 2.

Regression results for analysis predicting STOP latency as a function of positive symptoms, negative symptoms, and occupational functioning in patients.

	R	R Square	Adjusted R Square	Std. Error	β	F	p
PANSS Positive	0.491	0.241	0.194	26.250	0.491	5.086	.038*
PANSS Negative	0.111	0.012	-0.050	29.950	0.111	0.198	0.662
SFS Occupation	0.536	0.287	0.243	25.440	-0.579	6.443	.022*

*Note: * p <.05*

Table 3.

Regression results for analysis predicting positive symptoms in patients as a function of FA in each tract.

	R	R Square	Adjusted R Square	Std. Error	β	F	p
FA in V1-TPJ	0.352	0.124	0.069	5.149	-0.352	2.27	0.151
FA in TPJ-IFC	0.588	0.345	0.305	4.45	-0.588	8.450	.010*
FA in IFC-SEF	0.416	0.173	0.121	5.00	-0.416	3.348	0.086

*Note: * p <.05*

Table 4.

Regression results for analysis predicting negative symptoms in patients as a function of FA in each tract.

	R	R Square	Adjusted R Square	Std. Error	β	F	p
FA in V1-TPJ	0.026	0.001	-0.062	6.800	0.026	0.101	0.920
FA in TPJ-IFC	0.224	0.050	-0.009	6.630	-0.224	0.842	0.373
FA in IFC-SEF	0.244	0.059	0.001	6.598	-0.244	1.012	0.329

Table 5.

Regression results for analysis predicting occupational outcomes in patients as a function of FA in each tract.

	R	R Square	Adjusted R Square	Std. Error	β	F	p
FA in V1-TPJ	0.123	0.015	-0.047	10.909	0.123	0.244	0.628
FA in TPJ-IFC	0.429	0.184	0.133	9.928	0.429	3.614	0.075
FA in IFC-SEF	0.408	0.167	0.115	10.034	0.408	3.202	0.092

Table 6.

Multiple regression results for analyses predicting STOP latency as a function of FA in V1-TPJ, group, and the interaction between FA and group.

	b	β	t	p
Intercept	143.25	--	4.08	--
FA in V1-TPJ (centered)	454.64	0.62	0.42	0.674
Group	11.04	0.23	0.47	0.645
Interaction	-328.93	-0.68	-0.46	0.650

Table 7.

Multiple regression results for analyses predicting STOP latency as a function of FA in TPJ-IFC, group, and the interaction between FA and group.

	b	β	t	p
Intercept	146.36	--	11.25	--
FA in TPJ-IFC (centered)	977.25	0.74	1.28	0.211
Group	13.55	0.28	1.64	0.110
Interaction	-636.00	-0.81	-1.39	0.173

Table 8.

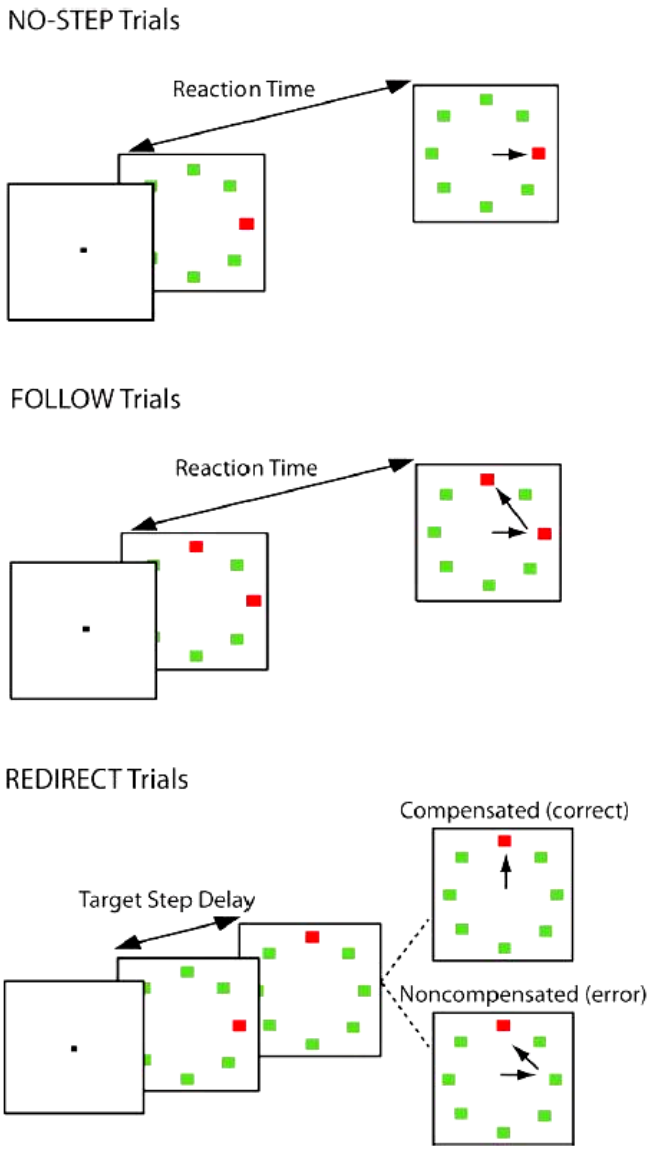
Multiple regression results for analyses predicting STOP latency as a function of FA in IFC-SEF, group, and the interaction between FA and group.

	b	β	t	p
Intercept	156.63	--	10.03	--
FA in IFC-SEF (centered)	-446.78	-0.34	-1.51	0.140
Group	5.32	0.11	0.51	0.610
Interaction	73.89	0.09	0.45	0.659

APPENDIX B: Figures

Figure 1.

Search Step Task.

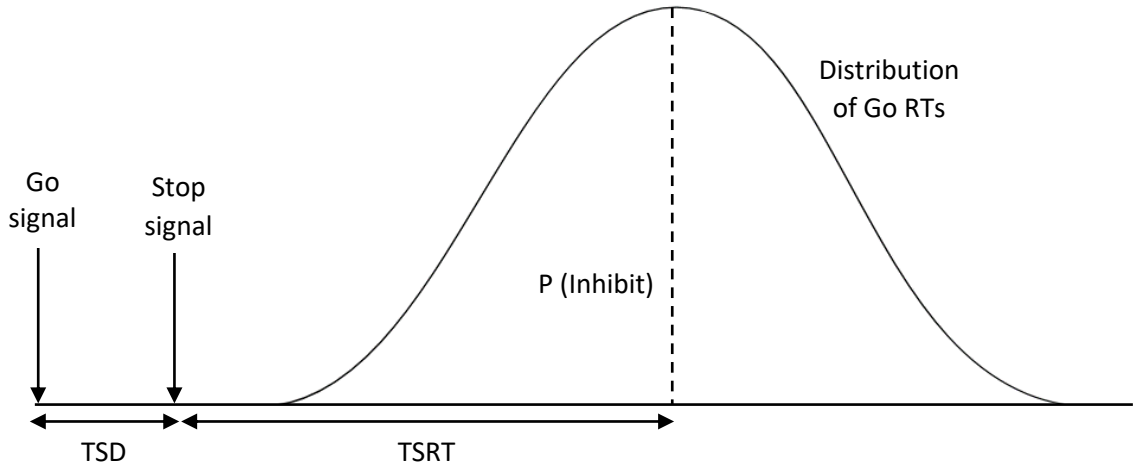


Reprinted from "Speed of Saccade Execution and Inhibition Associated With Fractional Anisotropy in Distinct Fronto-Frontal and Fronto-Striatal White Matter Pathways," by K. N. Thakkar, F.M.Z. van den Heiligenberg, R.S. Kahn, & S.F.W. Neggers, (2016). Human Brain Mapping, 37(8), 2811–2822. Reprinted with permission.

Note: An eight-element search array was desplayed on the screen. On no-step trials, the participant was instructed to look directly at the red singleton among green distractors. On redirect trials, the red singleton jumped to a new location and participants were instructed to inhibit their initial saccade and look directly at the new location. In follow trials, two red targets simultaneously appeared among green distractors and participants were instructed to look at each red target in succession (the order was not important).

Figure 2.

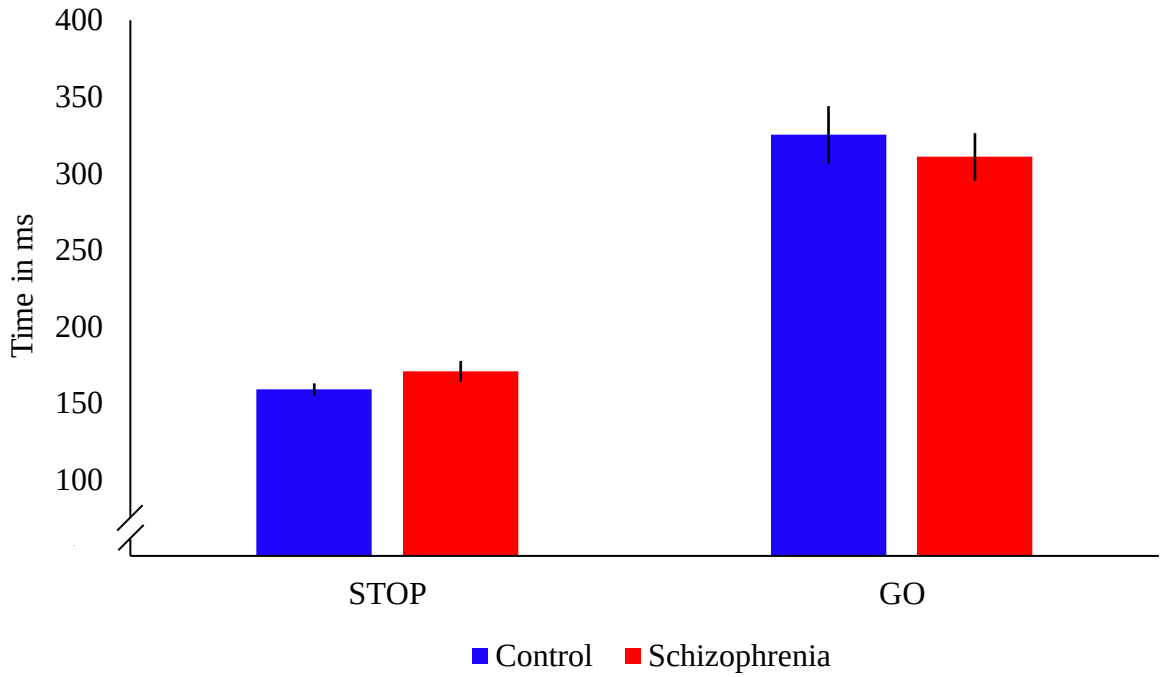
Calculating TSRT.



Note: This is an example figure of how TSRT would be calculated if the subject was able to inhibit his/her response 50% of the time at this particular TSD.

Figure 3.

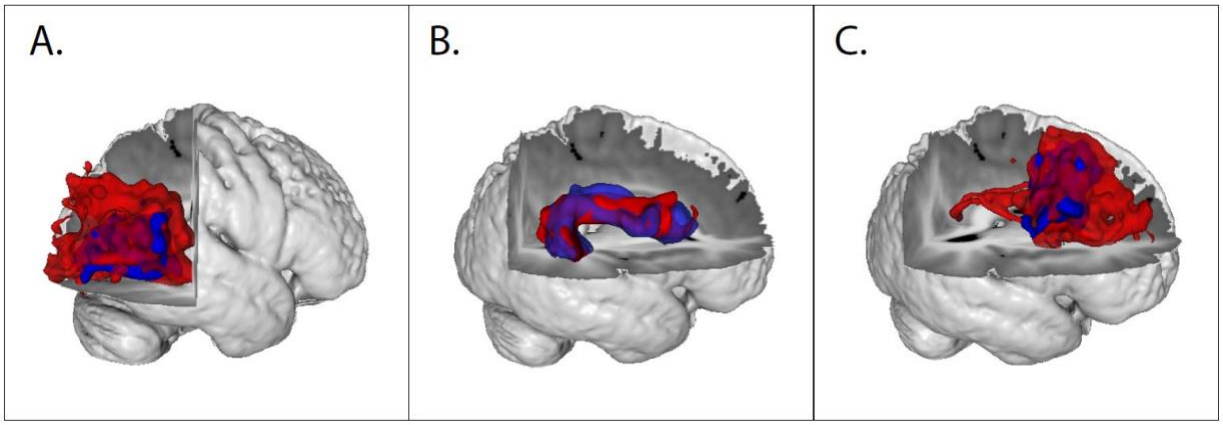
Mean reaction times for both STOP and GO processes.



Note: Bars represent standard error.

Figure 4.

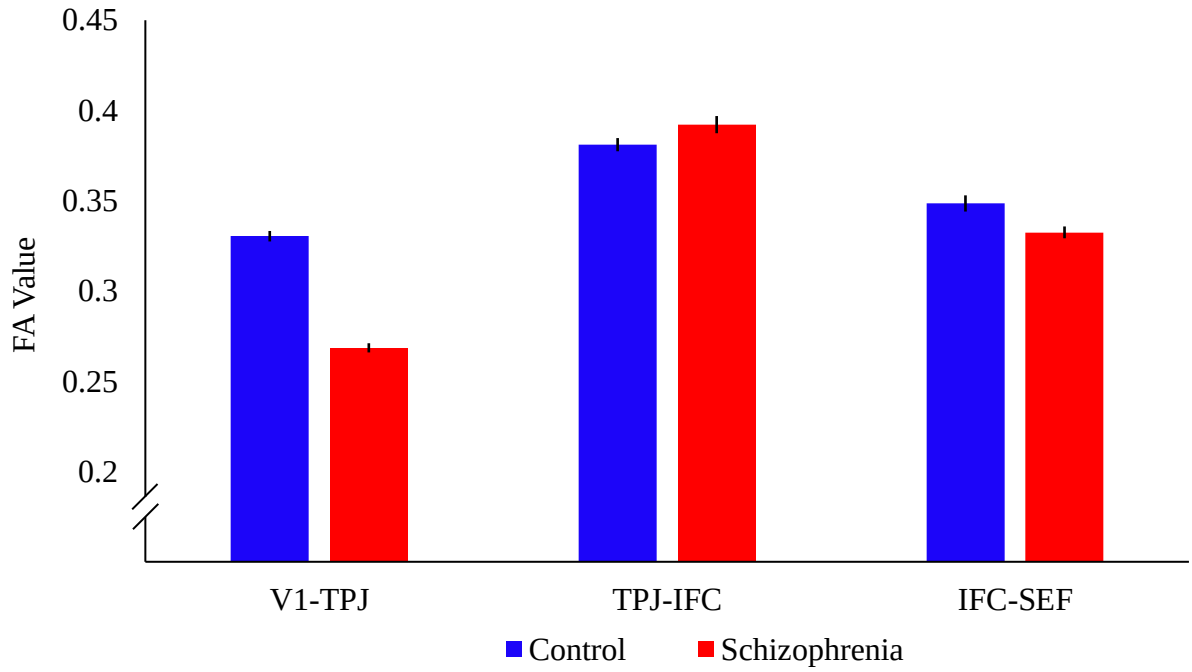
DTI visualization.



Note: 3D images of DTI tracts. Healthy control tracts are in blue; Schizophrenia tracts are in red. (A) V1-TPJ, (B) TPJ-IFC, (C) IFC-SEF

Figure 5.

Mean FA values in each tract for both groups.



Note: Bars represent standard error.

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