ABSTRACT

MANOUELA VESSELINOVA VALTCHEVA
Neural Activation Differences in a Model of Cognitive Control: an fMRI Study of Good and Poor Performers During Saccade Tasks
(Under the Direction of JENNIFER MCDOWELL)

Cognitive control is responsible for planning, cognitive flexibility, working memory, and inhibition. The antisaccade task is a good measure of inhibition as it requires the subject to inhibit looking at a peripheral target, and to generate a saccade (a quick eye movement) to the mirror image location of the stimulus. People with schizophrenia perform normally on simple refixation tasks (prosaccades) but make more antisaccade errors than control subjects. Imaging studies indicate reduced prefrontal cortex (PFC) and related circuitry activation during antisaccades in schizophrenia. Such dysfunction may be associated with poor performance on tasks requiring inhibition and working memory, generally, not just among people with schizophrenia. This study investigated differences in neural activation patterns between good and poor performers of the antisaccade task. Subjects were placed in a 1.5 T MR scanner while performing three tasks: antisaccade-fixation, prosaccade-fixation, and antisaccade-prosaccade. Functional MRI data were obtained for 30 subjects (69% female, M=19.6 (SD=2.1) years, 100% right handed), representing the top and bottom third of an antisaccade proportion correct distribution (N=114). Data were assessed using whole brain and region of interest (ROI) analyses. Good performers demonstrated robust anti- and prosaccade-related activation during antisaccade-fixation and prosaccade-fixation, respectively, while poor performers displayed reduced activation during both. ROI analyses demonstrated significant differences between the two groups during antisaccades but not during prosaccades. Neither group demonstrated significant percent signal change during the antisaccade-prosaccade task. Reduced activation in poor performers may be associated with more antisaccade errors and may be due to a reduced signal to noise ratio.

INDEX WORDS: cognitive control, fMRI, saccades, antisaccades, ROI

NEURAL ACTIVATION DIFFERENCES IN A MODEL OF COGNITIVE CONTROL: AN FMRI STUDY OF GOOD AND POOR PERFORMERS DURING SACCADE TASKS

by

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DEDICATION

To my family

I would not be here without their love, support, and the many sacrifices they have made throughout their lives in order to bring me to this country and ensure that I have the best opportunity to be happy and successful.

ACKNOWLEDGEMENTS

The completion of this thesis would not have been possible without the guidance of my research mentor Dr. Jennifer McDowell. The opportunity to work in her laboratory for the last three years of my undergraduate career was invaluable to my growth as a scientist and an individual. She challenged and encouraged me in all of my research- and career-related pursuits, while always lending her support. I would also like to thank Mr. Benjamin Austin for his invaluable help during data analysis, Ms. Cindy Krafft, Dr. Brett Clementz, and all the other members of the Clinical and Cognitive Neuroscience Laboratory. My research experience would not have been the same without the interest, support, effort, and friendship everyone had to offer. Thanks also go to UCSD and NARSAD for support during data collection.

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CHAPTER 1
INTRODUCTION

Background and Significance

Cognitive control is an important part of executive function which is responsible for key behaviors such as planning, cognitive flexibility, abstract thinking, rule acquisition, and inhibition of inappropriate responses. Such processes are adversely affected in schizophrenia, a severe and debilitating psychiatric disease that affects approximately 0.75% of the world's population. While positive symptoms such as hallucinations and delusions can be improved with pharmacological therapy, negative and cognitive symptoms such as restricted affect, anhedonia, and avolition show little improvement (Robinson, Woerner, Delman, & Kane, 2005). Research indicates that it is these negative and cognitive symptoms that may contribute most to poor quality of life and social and occupational dysfunction (Bow-Thomas, Velligan, Miller, & Olsen, 1999; Velligan, Alphs, Lancaster, Morlock, & Mintz, 2009; Velligan, et al., 1997). A more complete understanding of the dysfunctional neural mechanisms involved in the disease could prove advantageous in development of more comprehensive and effective treatments. This is where investigating the major differences in brain function responsible for executive control between people with and without schizophrenia can play a key role.

People with schizophrenia show specific deficits on eye movement tasks when compared to normal participants. More specifically, saccadic performance on simple versus more complex tasks has demonstrated differences between schizophrenia and normal subjects (Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; Katsanis, Kortenkamp, Iacono, & Grove, 1997).

Saccades are fast redirections of gaze that involve the movement of both eyes to a visual stimulus location. Manipulations of the saccadic system using different types of tasks have provided effective models of cognitive control for several reasons. First, the system is well understood based on extensive literature that ranges from single-unit recordings in primates (Johnston & Everling, 2008) to lesion studies in humans (Pierrot-Deseilligny, Milea, & Muri, 2004). Second, there is good convergence between the literature and human functional neuroimaging studies. Third, saccades can be measured precisely and with a number of reliable parameters such as response latency (reaction time), amplitude, and response percent correct (Smyrnis, 2008).

Saccade tasks can range from reflexive to more purposeful and cognitively complex. Specifically, prosaccades are more 'automatic' as they require a participant to simply look to a stimulus which appears on either side of the periphery. Antisaccades, on the other hand, are more 'purposeful' as they require redirection of a gaze to the opposite location of a target (Leigh & Zee, 1999). This is performed by first successfully inhibiting a saccade toward the stimulus when it appears in the periphery, and subsequently generating a saccade to the mirror image location (opposite side, same distance from the center). The greater cognitive complexity of an antisaccade stems from the necessity to maintain instruction during the task, inhibit a reflexive response towards the cue, and use visuo-spatial information to generate a saccade with correct amplitude to the mirror location of the cue. An error during this task is defined as an initial saccade toward the stimulus in the periphery.

Studies of antisaccade performance in schizophrenia indicate significantly more errors are made because the participants have difficulty inhibiting the initial glance toward the target that

appears in the periphery before looking to the mirror image location (Calkins, Iacono, & Curtis, 2003; Curtis, Calkins, Grove, Feil, & Iacono, 2001; Ettinger, et al., 2004; Ettinger, et al., 2006; McDowell, Myles-Worsley, Coon, Byerley, & Clementz, 1999). Furthermore, they demonstrate increased latencies and decreased spatial accuracy of correct responses (Ettinger, et al., 2004; Ettinger, et al., 2006). The high frequency of self-corrections of inhibitory errors indicates that the subjects understand the task instructions, but are unable to consciously inhibit inappropriate responses. Interestingly enough, first degree relatives of schizophrenia subjects also make more errors on cognitively complex tasks such antisaccades (Camchong, Dyckman, Austin, Clementz, & McDowell, 2008; Crawford, et al., 1998; McDowell, et al., 1999; Thaker, et al., 2000). This has led to the identification of poor antisaccade performance as a putative endophenotype for the disease, as it affects both people with schizophrenia and those who are genetically predisposed (Radant, et al., 2007).

Functional Magnetic Resonance Imaging (fMRI) has been used to assess patterns of activation of specific neural regions during saccade tasks. This method uses blood oxygenation level dependent (BOLD) signal to pinpoint increased metabolic activity within the brain. It is believed that neural activation of certain brain regions results in vasodilation to meet the metabolic demands of that area. As a result, there is an increase in blood volume and flow of oxygenated blood to the region. Because there is far more oxygenated blood than cerebral oxygen consumption, there is an increase in the ratio of oxygenated to deoxygenated blood. Deoxygenated blood is paramagnetic, causing a decrease in BOLD signal. Conversely, an increase in the ratio of oxygenated blood leads to an increase in BOLD signal. FMRI measures BOLD signal relative to a baseline condition in order to subtract out the basic neural blood flow

associated with the baseline task. In eye-movement studies, the baseline condition is often fixation, which alternates with blocks of the condition of interest (e.g. antisaccades). This is believed to allow the hemodynamic response in the brain to return to baseline and recover before the next block of task trials (McDowell & Clementz, 2001).

There are specific neural regions recruited for proper saccade generation. Previous imaging (McDowell, et al., 2002; O'Driscoll, et al., 1995; Paus, 1996; Raemaekers, et al., 2002; Sweeney, et al., 1996), animal (Bruce, Goldberg, Bushnell, & Stanton, 1985; Funahashi, Chafee, & Goldman-Rakic, 1993; Schlag-Rey, Amador, Sanchez, & Schlag, 1997), and lesion studies (Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, et al., 2003) have shown that the neural network involved in prosaccade generation includes the striatum, thalamus, superior colliculus (SC), frontal eye fields (FEF), supplementary eye fields (SEF), posterior parietal cortex (PPC), and primary visual and extrastriate cortex (McDowell, Dyckman, Austin, & Clementz, 2008). Brain activity during antisaccades demonstrates recruitment of other neural regions in addition to stronger activation of the basic circuitry required for prosaccades (Munoz & Everling, 2004; Pierrot-Deseilligny, Muri, Nyffeler, & Milea, 2005; Sweeney, Luna, Keedy, McDowell, & Clementz, 2007). Specifically, fMRI studies have shown increased prefrontal cortex (PFC) activation which is not seen during prosaccades (DeSouza, Menon, & Everling, 2003; Matsuda, et al., 2004; McDowell, et al., 2002). It is believed that this region is important for mediating the more cognitively complex behaviors such as attention, planning, spatial orientation, and inhibition that are required to perform the antisaccade task correctly (Goldman-Rakic, 1995; Miller & Cohen, 2001). Lesion studies demonstrate more antisaccade errors made by patients with damage to the DLPFC, but no increase in prosaccade errors when FEF, SEF, and PPC are

intact (Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, et al., 2003; Pierrot-Deseilligny, Muri, Ploner, Gaymard, & Rivaud-Pechoux, 2003).

Other behavioral and imaging studies have also investigated the effect of context on saccadic performance and neural activation (Dyckman, Camchong, Clementz, & McDowell, 2007). In those studies, neural activation patterns were compared between tasks with alternating blocks of antisaccade-fixation, prosaccade-fixation, and antisaccade-prosaccade. Antisaccade-fixation resulted in significantly greater percent signal change in the striatum, thalamus, PPC, FEF, SEF, and PFC when compared to prosaccade-fixation. During antisaccade-prosaccade tasks, where blocks of prosaccades alternate with blocks of antisaccades with no blocks of fixation, greater activation was observed only in PPC (precuneus, specifically), SEF, and FEF. Therefore, fewer regions showed antisaccade-related differences during the mixed task than when the single tasks were compared. These differences may be due to the increased level of difficulty of the antisaccade-prosaccade task. Because the subjects have to use working memory in order to maintain instructions for two active tasks, neural circuitry necessary for more than sole saccade generation has to be recruited. This demonstrates a context effect - neural activation for a saccade task will vary based on how the task is presented.

FMRI studies of eye movements and schizophrenia indicate differences in neural activation patterns when compared to normal subjects (Camchong, et al., 2008; Hill, et al., 2004). The normal prosaccade performance demonstrated by schizophrenia subjects is associated with an intact and functioning prosaccade neural circuitry (Clementz, McDowell, & Zisook, 1994; Crawford, Haeger, Kennard, Reveley, & Henderson, 1995; Ettinger, et al., 2006; McDowell & Clementz, 1997). Conversely, fMRI studies of poor antisaccade performance in

schizophrenia indicate reduced activation in basic saccade circuitry and PFC (Ford, Goltz, Brown, & Everling, 2005; McDowell, et al., 2002). Similar patterns of reduced activation are also seen in first-degree relatives of schizophrenia participants (Camchong, et al., 2008; Raemaekers, Ramsey, Vink, van den Heuvel, & Kahn, 2006). This indicates that the behavioral endophenotype of antisaccade errors is also associated with a specific deficit in neural circuitry activation necessary for inhibition.

While numerous studies report such differences in antisaccade performance and neural activation between schizophrenia and normal participants, healthy participants have also been shown to make errors on the task. This is especially seen in participants selected for low cognitive control on other tasks testing working memory in the face of distraction. These individuals show mild performance deviations during antisaccade tasks that can be further amplified if the task is presented in an interleaved form (antisaccades and prosaccades in the same run) (Unsworth et al., 2004). Such increase in error rates could be because low cognitive control participants are more prone to distraction and less likely to maintain task goals. Furthermore, previous fMRI studies of cognitive control using a working memory model show that healthy participants demonstrating high cognitive control strongly activate PFC and anterior cingulate cortex, while those scoring low weakly activate these regions (Kondo et al., 2004). This variability in performance points to questions about basic differences in neural circuitry activation that may lead to such behavioral differences among healthy participants during saccade tasks.

As such, it would be interesting to investigate whether the behavioral phenotype of poor antisaccade performance is associated with similar patterns of neural circuitry dysfunction in

normal participants. The current study aimed to answer this question by investigating neural circuitry activation in good and poor performers of the antisaccade task by applying fMRI analysis of data collected during antisaccade-fixation, prosaccade-fixation, and antisaccade-prosaccade trials.

Hypotheses

It was hypothesized that 1) there will be differences in neural activation patterns between good and poor performers during the antisaccade tasks (Performance effects), 2) different patterns of region activation will be observed during antisaccade-fixation versus antisaccade-prosaccade trials (Context effects), and 3) poor performers will demonstrate patterns of neural activation dysfunction similar to those observed in schizophrenia (i.e. reduced PFC and other saccade-related circuitry activation).

CHAPTER 2
MATERIALS AND METHODS

Overview

The current study is an analysis of fMRI data collected at the University of California, San Diego. 114 normal undergraduate students were tested on the antisaccade task and those who scored in the top and bottom 30% of the proportion of correct antisaccades distribution returned for a second fMRI session. Imaging data was collected for both groups while they performed three types of tasks: antisaccade-fixation, prosaccade-fixation, and antisaccade-prosaccade tasks. The fMRI data were analyzed to evaluate brain activity differences in prefrontal cortex and other regions between the two groups of good- and poor-performing subjects. Activity in previously identified regions of interest (ROIs) were evaluated and compared between groups as well.

Participants

Undergraduate participants (N=114, 100% right handed) were recruited from the University of California, San Diego. All participants were screened for personal and family psychiatric history and medical history including neurological hard signs or history of head trauma. They were free of contraindications for fMRI, eliminated for conditions such as pregnant, claustrophobic, or having a pacemaker, shrapnel, other metal, aortic clips, prosthesis, heart valve replacement, or IUD. Participants then were evaluated on behavioral antisaccade performance. Those scoring in the top and bottom 30% of the proportion of correct antisaccades

distribution were asked to return for a second fMRI session (N=30 , 69% female, age M=19.6 years, SD=2.1 years). There were 16 good performers and 14 poor performers.

Behavioral Testing

Eye movements were recorded using infrared oculography in a laboratory in the Psychology department. Antisaccade performance was assessed on 100 antisaccade trials and proportion correct was quantified. Sixteen subjects scoring in the top third and 14 subjects scoring in the bottom third of the antisaccade performance distribution practiced on the stimuli before entering the MRI scanner.

Imaging data were collected during three eye movement tasks: antisaccade-fixation, prosaccade-fixation, and a mixed antisaccade-prosaccade task. Stimuli were presented in a block design, alternating between blocks of antisaccades or prosaccades and fixation. During the mixed condition there was no fixation and blocks of antisaccades alternated with blocks of prosaccades. The total duration for each of the three task types was 315 seconds (5 min 15 sec).

During the antisaccade-fixation task (see Figure 1), 7 blocks of antisaccades alternated with 8 blocks of fixation for a total of 15 blocks per task run. Specifically, 7 antisaccade trials per 21 second block alternated with a 21 second block of fixation. The visual stimulus was a five-pointed star that appeared in the center of the visual field and changed color to indicate task type. Purple color indicated fixation and blue color indicated an antisaccade trial was about to begin. During fixation, participants were asked to look at the fixation cue at the center of the screen (0 degrees) and maintain looking at the center even if the fixation cue moved to the periphery. During antisaccades, participants were instructed to not look at the blue star when it moved to

the periphery, but instead to look to the mirror image location (opposite side, same distance from the center) as quickly and accurately as possible. An error was an initial saccade toward the stimulus.

During the prosaccade-fixation task (see Figure 2), 7 blocks of prosaccades alternated with 8 blocks of fixation for a total of 15 blocks per run. There were 10 prosaccade trials per 21 second block alternating with 21 second blocks of fixation. The visual stimulus during this task was again a purple star for fixation that changed to a yellow star to indicate prosaccades. For prosaccades, participants were instructed to simply follow the yellow star with their eyes as quickly and accurately as possible.

The antisaccade-prosaccade mixed condition consisted of alternating sets of 10 prosaccades per 21 second block, and 7 antisaccade trials per 21 second block. Visual stimuli alternated between yellow star for prosaccades and blue star for antisaccades. The same previously described instructions were given for prosaccades and antisaccades.

Imaging

A 1.5 T Siemen's MRI scanner at UCSD Thornton Hospital was used to obtain high resolution structural, and lower resolution functional, data during all three task types. During imaging, participants were provided with earplugs and arranged in a supine position. Their heads were stabilized with foam padding and head restraints, and a dual mirror box was placed above and in front of the participants' eyes, designed to make the stimuli visible to the participants and their eyes visible to an eye-tracking camera. During the tasks, eye movements were recorded with MRI compatible equipment (MeyeTrack LR, SensoMotoric Instruments, Inc., Berlin,

Germany). The eye was illuminated via an infrared light source and displayed in an image via a remote infrared camera with long-range optics. Eye movements were displayed so performance could be monitored and recorded. An LCD Projector displayed stimuli onto a rear projection screen using software programmed locally.

Structural images were obtained using a standard T1-weighted high resolution structural scan (3DMPRAGE, 128 mm slab, 1x1x1 mm voxels, repetition time [TR]=11.45, echo time [TE]=4.4, flip angle=10 degrees). T2*-weighted functional gradient recalled echo planar images (32 continuous axial slices, 4 mm isotropic, TR=3 sec, TE=40 msec, flip angle=90 degrees) were acquired during saccadic performance.

FMRI Data Analysis

Imaging data was analyzed using Analysis of Functional Neuroimages (AFNI) (Cox, 1996) software and methods similar to previously published data from the lab (Camchong, et al 2008; Dyckman, et al., 2007). Individual images were used to create three-dimensional datasets. For each run, all volumes were time corrected for slice acquisition order and then registered to the middle volume to correct for minor head movement over time (3dvolreg) and spikes were removed using 3dDespike. A full width, half-maximum (FWHM) Gaussian filter (4mm) was applied to each dataset to account for individual variations in anatomy. For each voxel, the percent change in BOLD signal between baseline (fixation) and experimental condition (pro-or antisaccades) blocks was calculated for each of the time points. For each subject, a multiple regression model (3dDeconvolve) was used to analyze the time series data for each run. In this model, the task regressor of interest (the model of hemodynamic response function) and five

nuisance regressors (roll, pitch, yaw (to account for residual head motion), and baseline and linear trends (to eliminate slow signal drifts)) were entered into a linear multiple regression to evaluate BOLD signal change associated with the experimental conditions. Percent signal change was calculated by dividing the regressor of interest by the baseline regressor. Anatomical and functional data were transformed to standardized Talairach space (Talairach & Tournoux).

To display saccade-related BOLD signal change, data from all participants in all groups across runs were submitted to a one-sample *t* test on a voxel-by-voxel basis. To protect against false positives, a threshold/cluster method derived from Monte Carlo simulations (accounting for the 4mm FWHM Gaussian filter with a connectivity radius of 5.7 mm; on the basis of these simulations, the family-wise α of 0.05 was preserved with an a priori voxel-wise probability of 0.025 and three-dimensional clusters with a minimum volume of 1152 μL (18 or more voxels)) was applied to the *t* map. The resulting averaged, clustered, one-sample *t* map showed BOLD signal changes associated with saccadic performance.

Region of interest (ROI) analysis was performed on the unclustered data from each group and for each task by using a map generated from a previously studied larger sample (Dyckman et al., 2007). Every voxel that matched the 20 previously identified ROIs was averaged for each participant, region, and task. A *t* test was performed to identify any significant differences in percent signal change for each ROI between good and poor performers.

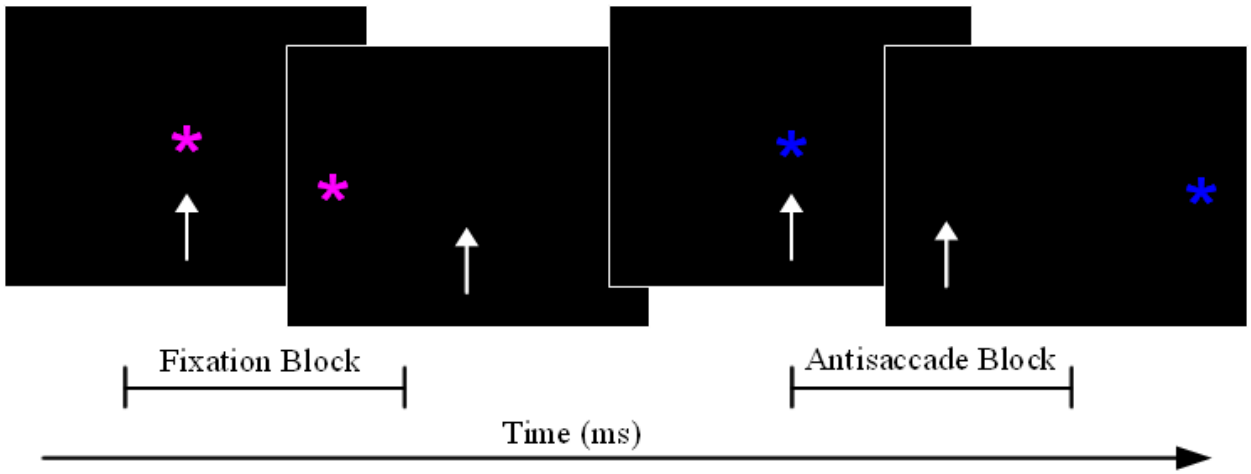

Figure 1: The antisaccade-fixation task alternated between blocks of fixation and blocks of antisaccade trials where the participants were required to inhibit looking at the peripherally presented stimulus and instead look to the mirror image location. The black boxes represent the stimulus presentation on a computer screen across time as seen by the participants. The white arrows indicate the correct eye position throughout time and are not present during the actual task.

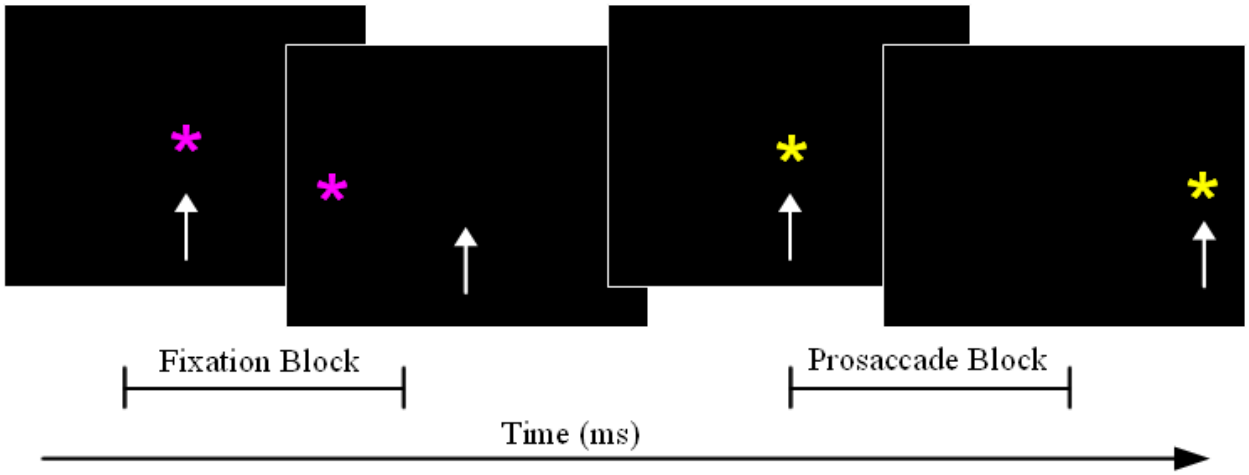

Figure 2: The prosaccade-fixation task alternated between blocks of fixation and blocks of prosaccade trials where the participants were instructed to simply follow the visual stimulus with their eyes as quickly and accurately as possible. The black boxes represent the stimulus presentation on a computer screen across time as seen by the participants. The white arrows indicate the correct eye position throughout time and are not present during the actual task.

CHAPTER 3
RESULTS

For this study, 30 healthy participants scoring in the top and bottom third of an antisaccade proportion correct distribution returned for a second fMRI session (16 good, 14 poor). Each participant performed three different types of tasks while in the scanner: antisaccades alternating with fixation, prosaccades alternating with fixation, and prosaccades alternating with antisaccades. FMRI data was analyzed using two methods. Whole brain analysis was used to identify clusters of increased BOLD percent signal change above significant levels. Previously identified ROIs were used to measure average percent signal change in each participant and collapsed across groups in order to compare good and poor performer saccadic circuitry activation. All functional maps are overlaid upon a representative anatomical brain for each group obtained by averaging each participant's standardized 3-dimensional anatomical data set.

Antisaccade-Fixation

During the antisaccade-fixation task, good performers displayed increased BOLD signal change when performing antisaccades (see Figure 3a). Specifically, there was significant antisaccade-related percent signal change in the occipital cortex, PPC, FEF, and SEF. Poor performers displayed decreased BOLD signal change in comparison to the good performers (see Figure 3b). Positive percent signal change in the poor performer group did not survive the clustering procedure. Activation of saccadic circuitry including PPC, FEF, and SEF could be

seen only when the threshold was reduced to well below what is statistically significant (see Figure 4).

Prosaccade-Fixation

Good performers displayed increased BOLD signal change when making prosaccades during the prosaccade-fixation task. There was significant prosaccade-related percent signal change in the occipital cortex, PPC, and FEF (see Figure 5a). Positive percent signal change did not survive clustering in the poor performer group during prosaccades (see Figure 5b), but when the threshold was reduced to below significant levels, activation was observed in occipital cortex, PPC, FEF, and SEF (see Figure 6).

Antisaccade-Prosaccade

Analysis of circuitry activation during the antisaccade-prosaccade mixed task demonstrated no positive signal percent change after clustering (not shown). Without clustering, at below significant levels, the good performers displayed increased activation that looked to be diffuse and random throughout the brain (see Figure 7). The poor performers did not display any task-associated positive percent signal change (not shown).

ROI Analyses

ROI analyses were performed using region data identified in a particularly large previous study on normal subjects engaged in a similar antisaccade task (see Table 1). During the antisaccade-fixation task good performers displayed significantly more positive percent signal

change than poor performers in numerous regions. Specifically, significantly stronger activation was seen when average percent signal change was collapsed across left and right inferior parietal cortex (IPL), left and right middle occipital cortex, left and right striatum, left and right thalamus, inferior frontal cortex (IFC), left and right PPC (cuneus and precuneus), left and right FEF (medial and lateral), and left and right PFC (see Figure 9). Average percent signal change of the poor performers centered around 0, except in the middle occipital cortex, PPC, and PFC. Specifically, in the middle occipital cortex and PFC, the poor performers demonstrated negative percent signal change, opposite to the trend in good performers. In the PPC, poor performers demonstrated positive percent signal change, similar to the good performers.

ROI analysis of good and poor performers during the prosaccade-fixation and antisaccade-prosaccade tasks indicated no significant differences in average percent signal change between the two groups (not shown).

In summary, whole brain analyses of the good and poor performers indicated several differences in neural activation patterns. Good performers displayed significant BOLD percent signal change during the antisaccade-fixation and prosaccade-fixation tasks, while poor performers demonstrated no significant percent signal change. Only when thresholds were reduced to below significant levels did the poor performers demonstrate basic saccade circuitry. No group demonstrated significant percent signal change during the antisaccade-prosaccade task. ROI analyses indicated significant differences between the two groups during antisaccade-fixation, but not during prosaccade-fixation and antisaccade-prosaccade tasks.

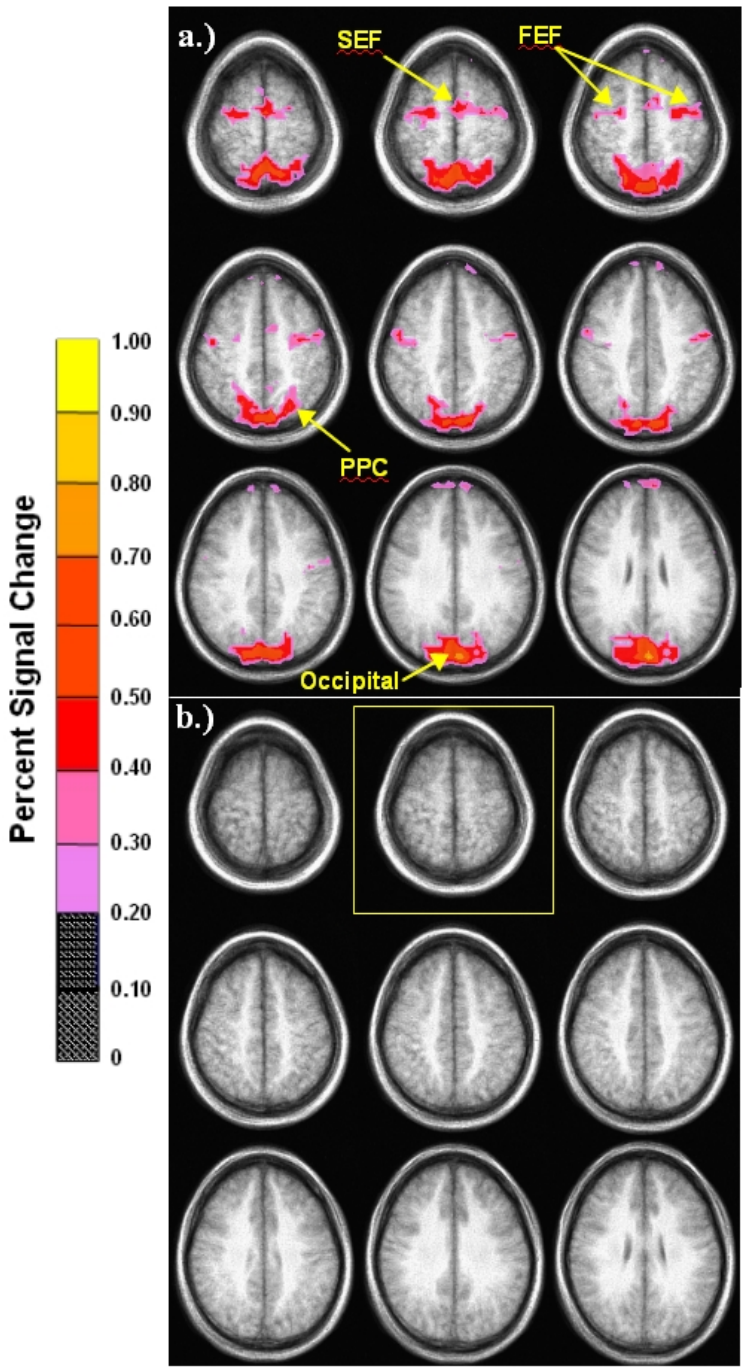

Figure 3. Antisaccade-related BOLD signal change. Colors from pink to yellow indicate increasing significant percent signal change. Each group is shown in 9 equally spaced axial slices throughout the brain using neurological convention (left hemisphere on left side).
a.) Antisaccade-related signal change collapsed across good performer group.

b.) Antisaccade-related signal change collapsed across poor performer group. Note there is no signal present.

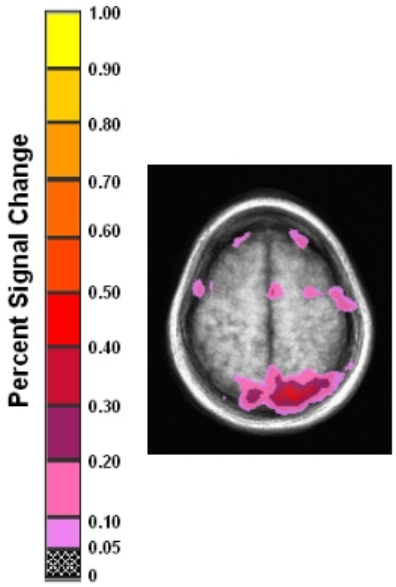

Figure 4. Antisaccade-related percent signal change in poor performer group with threshold reduced to below significant levels. Single axial slice corresponds to outlined slice in Figure 3b (top middle). Note presence of basic saccadic circuitry.

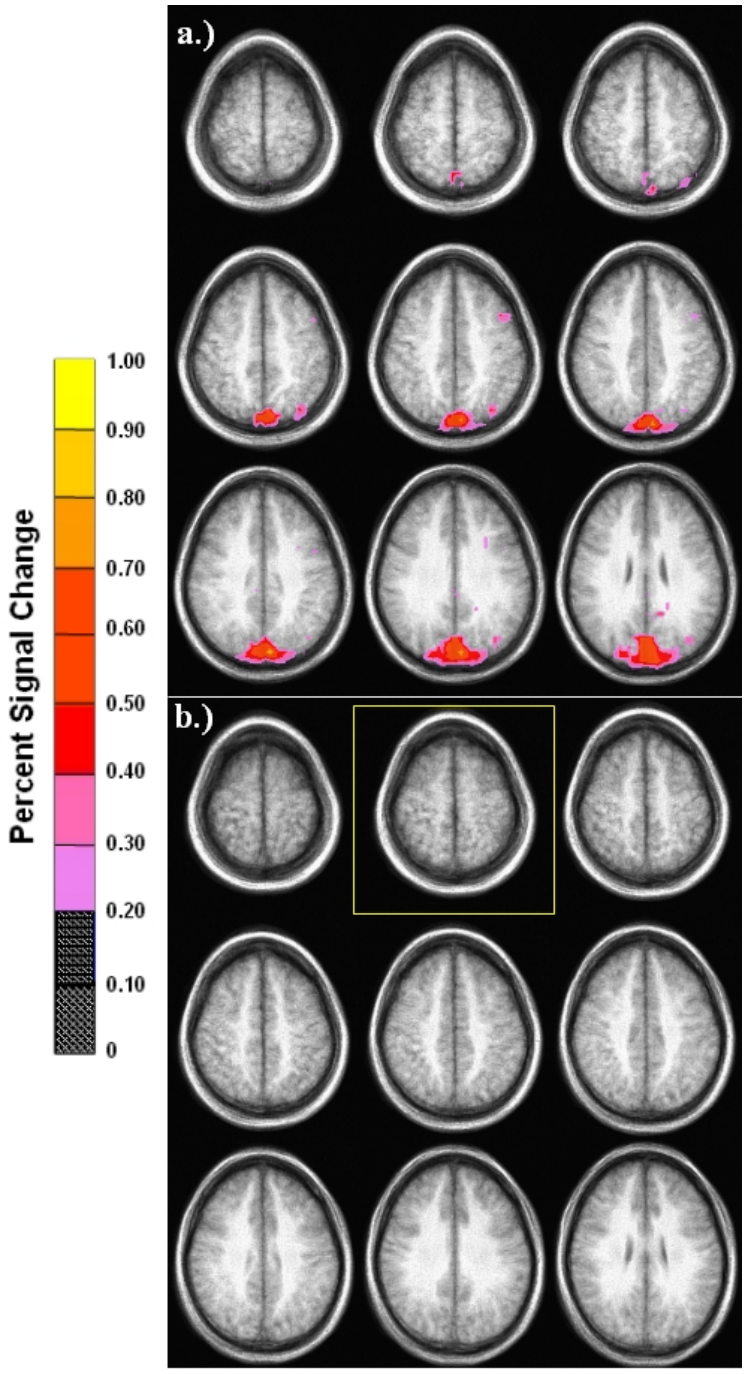

Figure 5. Prosaccade-related BOLD signal change. Colors from pink to yellow indicate increasing significant percent signal change. Each group is shown in 9 equally spaced axial slices throughout the brain using neurological convention (left hemisphere on left side).
a.) Prosaccade-related signal change collapsed across good performer group.

b.) Prosaccade-related signal change collapsed across poor performer group. Note there is no signal present.

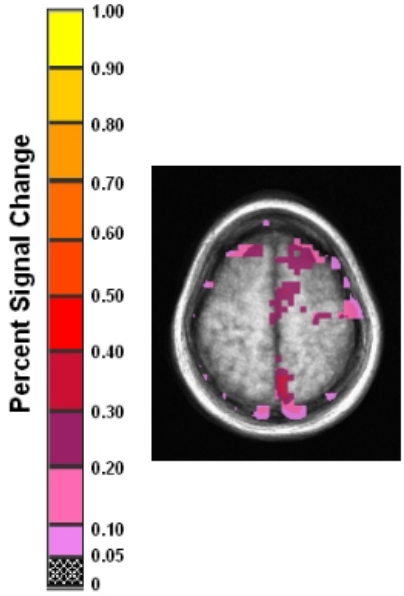

Figure 6. Prosaccade-related percent signal change in poor performer group with threshold reduced to below significant levels. Slice corresponds to outlined slice in Figure 5b and Figure 4. Note presence of some saccadic circuitry. (For viewing purposes, threshold was raised to t=0.693 at p=0.53.)

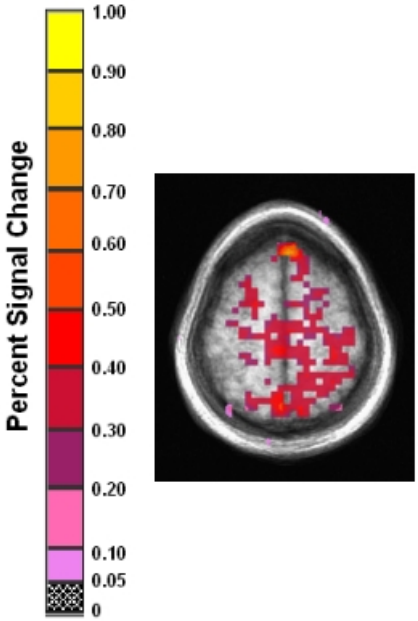

Figure 7. Percent signal change during pro-anti trials in good performer group with threshold reduced to below significant levels. Slice corresponds to same axial position as in Figures 4 and 6. Note presence of diffuse activation all throughout the brain. (For viewing purposes, threshold was raised to t=0.852 at p=0.41.)

Table 1. Talairach coordinates of the center of mass for each ROI. Regions represent areas that showed significant differences in BOLD signal across anti-fixation, pro-fixation, and pro-anti runs (Dyckman et al., 2007).

ROI	L/R	*X*	*Y*	*Z*
SEF		0	+1	+56
Lat FEF	L	-42	-4	+53
	R	+43	-7	+52
Med FEF	L	-26	-5	+53
	R	+26	-7	+52
PFC	L	-34	+34	+38
	R	+36	+43	+26
IFC	R	+37	+32	+1
Precuneus	L	-22	-59	+55
	R	+15	-60	+55
Cuneus	L	-14	-79	+7
	R	+10	-78	+7
IPL	L	-47	-31	+25
	R	+54	-42	+23
Middle Occ	L	-29	-85	+4
	R	+24	-87	+4
Striatum	L	-18	+1	+17
	R	+15	+2	+18
Thalamus	L	-13	-13	+12
	R	+10	-13	+14

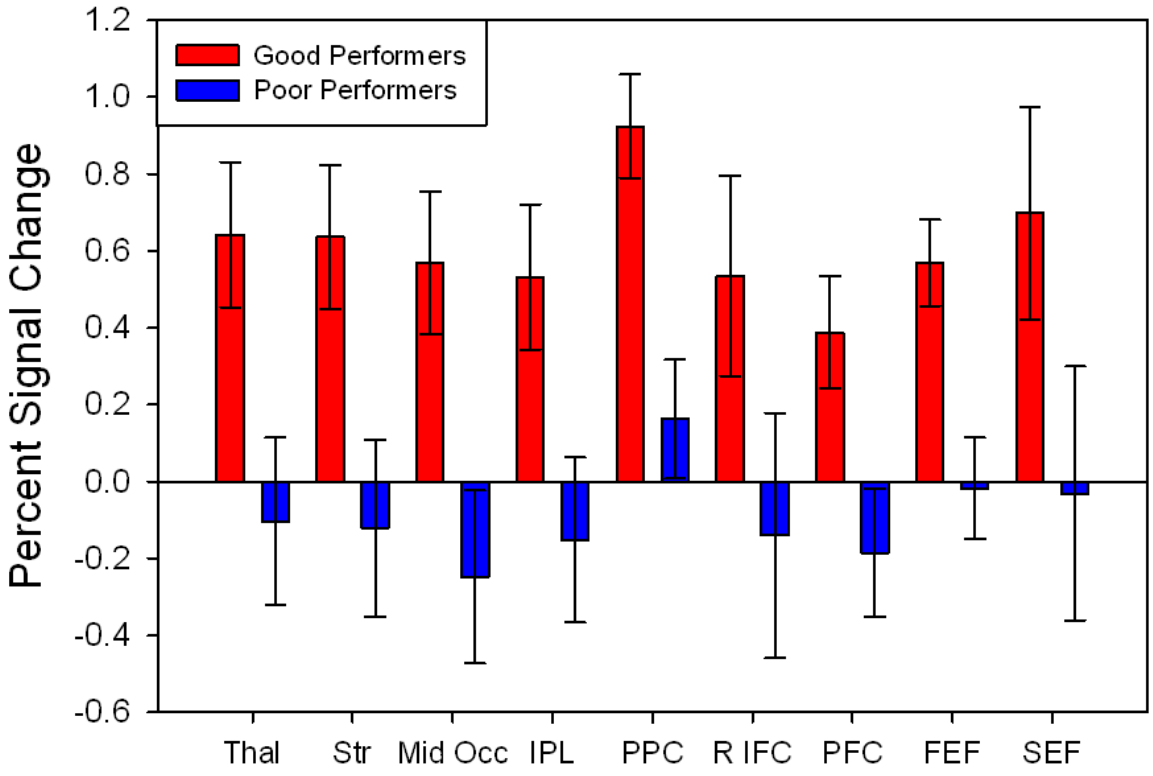

Figure 8. ROI analyses of antisaccade-related average percent signal change in good versus poor performers. Significant differences in BOLD percent signal change were found in thalamus (Thal), striatum (Str), middle occipital cortex (Mid Occ), IPL, PPC, right IFC, PFC, and FEF. Good performers (red) demonstrated a trend toward positive percent signal change. Poor performer percent signal change centered around 0 for all regions except the occiptial cortex, PPC, and PFC. In the occipital cortex and PFC poor performers demonstrated negative percent signal change, opposite to the good performers. In the PPC poor performers demonstrated positive percent signal change, similar to the good performers.

CHAPTER 4
DISCUSSION

The present study sought to investigate whether variation in cognitive control among normal participants is associated with differences in neural activity. Neural activation patterns during eye-movement tasks in good and poor performers of the antisaccade task who have no previous psychiatric history were examined. Specifically, differences in saccadic circuitry activation between the two groups were investigated using whole brain and ROI analyses. The subjects performed three different types of tasks: antisaccades paired with fixation (volitional), prosaccades paired with fixation (reflexive), and antisaccades alternating with prosaccades. Differences in neural activation patterns found can begin to address the source of performance variability in healthy subjects and context-dependent performance. Also, as previous studies have indicated a distinct neural circuitry dysfunction in people with schizophrenia during inhibitory tasks such as the antisaccade task, it was interesting to investigate whether similar dysfunction in patterns of activation could be observed in poor performers of the same task with no history of the disease.

The analysis of neural activation patterns in good and poor performers during the antisaccade-fixation task indicated significant differences between the two groups. In the good performer group, there was a significant increase in antisaccade-related BOLD percent signal change. Previously identified patterns of neural activation necessary for saccadic performance were demonstrated, except for PFC. This could be due to the fixation block which required the participants to maintain focus on the center of the screen, even when the fixation target moved.

In order to maintain fixation in the face of such distraction, the participants most likely had to maintain the basic rule of the task and inhibit a glance to the periphery, requiring use of some cognitive control circuitry as well. The poor performers did not display such positive activation at the significant level, but rather saccadic activation patterns could only be seen when the threshold was reduced to levels well below significance. ROI analyses using previously identified regions of activation important for saccadic performance also indicated a significant difference between the good and poor performer groups in all regions but SEF. Specifically, the good performers displayed a significant increase in percent signal change in supporting regions, while the poor performers demonstrated an average percent signal change around 0 in all regions but the middle occipital cortex, PPC, and PFC. In the middle occipital cortex and PFC the poor performer percent signal change was negative (opposite to the good performers). In the PPC, poor performers actually demonstrated an increase in percent signal change above 0, similar to the good performers but not as robust. The PPC is an important region for visuo-spatial attention processes and transformation of sensory input into a motor command and is more robustly activated during antisaccades. This positive activation may indicate less of a decrease in function of this region within the poor performers, but activation was still significantly more reduced than the change demonstrated by the good performers. Overall, the poor performers displayed a global reduction in activation of saccadic circuitry with the general pattern still intact. Such decreased activation in the poor performer group is likely to result in behavioral deficits such as a higher proportion of antisaccade errors. This supports the initial hypotheses predicting differences in neural activation patterns between good and poor performers. Furthermore, the

reduction in saccade circuitry activation is similar to that observed in schizophrenia, supporting the third hypothesis of the study.

Analysis of neural activation patterns during prosaccade-fixation also indicated some major differences between the good and poor performers. Only the good performer group showed activation of general saccadic circuitry after clustering, with increased BOLD percent signal change in the occipital cortex, PPC, and some lateral FEF. Poor performers showed a similar activation pattern only after the threshold was reduced to below statistically significant levels. These differences in general activation patterns are interesting because the prosaccade task is a simple refixation task, where good performance is demonstrated by both normal and schizophrenia participants. In this study, the poor performers demonstrated a generalized reduction in prosaccade-associated neural circuitry activation. Conversely, ROI analyses indicated no significant differences in average percent signal change between good and poor performers. This was expected, as schizophrenia participants perform normally on this task as well (Clementz, McDowell, & Zisook, 1994; Crawford, Haeger, Kennard, Reveley, & Henderson, 1995; Ettinger, et al., 2006; McDowell & Clementz, 1997).

Neither the good nor poor performer groups demonstrated BOLD percent signal change above significant levels during the mixed task of antisaccades alternating with prosaccades. This task aimed to look at the effect of context on neural circuitry activation by using an active baseline condition (prosaccades) instead of a more passive baseline (fixation). Neural circuitry activation during this task could highlight the major point of difference between the regions required to perform prosaccades versus antisaccades (i.e. PFC). However, previous studies of context-dependent performance have indicated that there is activation of higher level cognitive

processes such as SEF, FEF, and precuneus in order to maintain task switch instructions (Dyckman et al., 2007). Conversely, the data from this study demonstrated no significant clusters of activation in either group. Below significant levels there was a general diffuse activation throughout the good performer group, but the poor performer group did not display any positive activation (other than a few signal artifacts). ROI analysis indicated no significant differences in activation between good and poor performers.

These results may indicate the presence of a different context-dependent effect. The good performer group demonstrated clear positive percent signal change after clustering of the antisaccade-fixation data. However, no clusters survived the analysis of the mixed task. This difference may be due to differences in general circuitry activation dynamics. During the antisaccade-fixation, the fixation blocks provided a more passive baseline measure that allowed the hemodynamic response to recover so each antisaccade block essentially measured mostly antisaccade-related activity. In contrast, during the antisaccade-prosaccade mixed task, prosaccades provided an active baseline. Each task in this case required the activation of basic saccadic circuitry and even further cognitive effort to maintain the instructions. This constant activation of neural response may be the reason why no significant percent signal change was observed in either group of performers.

One of the major differences that can be noted between good and poor performers across all tasks is that the poor performers never presented activation at significant levels. Though they showed the presence of basic saccadic circuitry, it was not as robust as the activation seen in the good performer group. This generalized reduction in saccadic neural circuitry activation could be due to a decreased signal to noise ratio. Previous studies have demonstrated a decreased signal to

noise ratio in people with schizophrenia. It is hypothesized that this occurs because of a lack of local cortical network inhibition in the brain, which leads to an uncontrolled spread of activation and increase in neuronal spontaneous discharge within the neural networks. This results in decreased network specificity, reduced cortical assembly stability, and possibly in the unfocused PFC BOLD response seen in schizophrenia (Winterer & Weinberger, 2004). Within the current study, it is possible that the poor performers had a reduced signal to noise ratio when compared to the good performers, leading to less circuitry available for recruitment and activation that could reach significant threshold levels. This may be another point of similarity between the poor performer neural activation patterns demonstrated in this study and schizophrenia.

Another interesting point to consider regarding the significant differences in antisaccade circuitry activation between the good and poor performers is their background. Both groups have no previous familial or personal psychiatric history. Furthermore, they both come from a group that is considered to be high-functioning - undergraduate students at a large university. While the poor performers demonstrated a generalized decrease in neural activation during a cognitively complex task (a behavioral endophenotype similar to the disease state), this abnormality has not created any obvious disadvantages to their quality of life like those associated with schizophrenia.

Major differences between the findings of this study and previous fMRI studies of saccadic performance center around a lack of PFC signaling and lateralization in the current dataset. The major region activated preceding correct antisaccade performance in previous studies has been the right PFC. There was no major PFC activation identified during antisaccades of the good performer group after clustering, possibly because of a more complex fixation block.

Also, there were no significant PFC differences between good and poor performers in the initial ROI analysis, which used lateralization (right versus left, medial versus lateral) due to the previously identified regions (Dyckman et al., 2008). Significant differences between the groups were only identified when the anatomical regions were collapsed (right with left, medial with lateral). This could also explain why the only region that was not significantly different in activation between the two performer groups during antisaccade-fixation was the SEF, as it is located between the hemispheres. Further studies using a more robust sample size could provide better statistical power that could aid in identifying more specific regions of activation and group differences.

In summary, normal undergraduate participants underwent fMR imaging while performing three basic tasks that depended on saccadic circuitry. Whole brain analyses of good and poor performer groups demonstrated significant differences in neural activation during the antisaccade-fixation task and prosaccade-fixation task, but not during the mixed antisaccade-prosaccade task. Significant differences in percent signal change of saccadic performance-associated regions were found only during the antisaccade-fixation task. Overall, the poor performer group demonstrated a global decrease of saccadic circuitry activation, resulting in no positive percent signal change above significance thresholds. This may be due to a decreased signal to noise ratio, a neural activation characteristic associated with schizophrenia. Larger studies could gain more insight into the underlying neural causes of performance variation in normal participants during volitional saccades and provide a useful construct for studying neural bases of schizophrenia-related characteristics.

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