BEHAVIORAL AND NEURAL CORRELATES OF POOR SACCADIC CONTROL IN HEALTHY UNDERGRADUATES

by

MICHAEL THOMAS AMLUNG

(Under the Direction of Jennifer E. McDowell)

ABSTRACT

Correct antisaccade (AS) performance requires inhibition of a reflexive glance to a peripheral visual cue and generation of a saccade to its mirror image location. Patients with schizophrenia make an increased proportion of AS errors which are associated with prefrontal cortex (PFC) dysfunction. It is uncertain whether this relationship is specific to schizophrenia, or if decreased PFC activity is associated with increased AS errors in non-clinical samples. This study examined brain activation in two samples of healthy undergraduates who were selected based on good and poor AS performance. AS generation was associated with robust activity in the well-defined saccade circuitry that included bilateral PFC. Poor performers, however, had decreased BOLD activation in areas known to support inhibition and working memory. These data suggest that healthy people who show compromised inhibitory control may be more likely to show evidence of disregulation of PFC-mediated circuitry under conditions of increased task demand.

INDEX WORDS: antisaccade, prosaccade, inhibition, schizophrenia, fMRI
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CHAPTER 1
INTRODUCTION

Schizophrenia is a debilitating psychiatric illness that is characterized by symptoms that are remarkably similar across cultures (Jablensky et al., 1992). Fortunately, modern pharmacological treatments are somewhat effective at alleviating these symptoms in many patients (Remington & Kapur, 2000). Achieving a better understanding of the etiological factors of schizophrenia, nonetheless, is an important area of ongoing research. The potential impact of this work is widespread. First and foremost, better characterization of the underlying abnormalities in schizophrenia could spawn the development of more effective pharmacological treatments. Moreover, this research may identify potential targets for early intervention that could prevent the progression of the disease.

In recent decades, considerable advances have been made in delineating the clinical, cognitive, and neurobiological disturbances that characterize various stages of the illness (e.g. Kurtz, 2005; Ross et al., 2006; Walker et al., 2004). An important complement to these illness-based studies is the recent emphasis on understanding the factors that place certain individuals at high-risk for developing psychosis (Braff et al., 2007; Miller & Yee, 1994). Focusing efforts on understanding the neural substrates of schizophrenia-like phenotypes in these at-risk samples is particularly informative for understanding the neuropathology of schizophrenia.

Of the myriad cognitive disturbances present in schizophrenia, deficits in cognitive control and working memory have important implications for daily functioning. The ability to flexibly control behavior is crucial for navigating daily life. Additionally, problems inhibiting unwanted behaviors—as commonly seen in schizophrenia—can have an adverse impact on
social and interpersonal interactions. These deficits are of particular importance for etiological studies as persons with the illness, their biological relatives, and healthy individuals who are psychometrically identified as psychosis-prone show similar behavioral abnormalities on laboratory tasks measuring response inhibition. These findings support the hypothesis that inhibitory deficits may serve as a viable endophenotype for schizophrenia (e.g. Calkins et al., 2008; McDowell et al., 1999; Turetsky et al., 2007).

Saccadic Eye Movements: Behavior and Neural Correlates

One class of tasks that has been extensively used to study differences in cognitive control and working memory processes is saccadic eye movements. Saccades are rapid redirections of gaze that serve to foveate a location or object of interest and exist in a hierarchy of increasingly complex behavior (Leigh & Zee, 2006). In the laboratory, saccades range from reflexive (e.g. prosaccades), which require an eye movement to the location of a peripheral stimulus to more volitional (e.g. antisaccades; Hallett, 1978), which require inhibition of a glance towards a peripheral stimulus and subsequent generation of a saccade in the opposite direction. The prototypical antisaccade task used in the laboratory requires redirection of gaze from central fixation to the mirror image location (same distance, opposite direction) of a peripheral cue, without first looking at the cue itself. An initial glance towards the cue constitutes an error and is construed as a failure of inhibition.

The neural architecture supporting saccadic eye movements has been well characterized through animal neurophysiology, human lesion, and neuroimaging studies (see Figure 1.1; for recent reviews in these areas see Johnston & Everling, 2008; Muri & Nyffeler, 2008; and McDowell et al., 2008, respectively). A general overview of saccade circuitry is first presented,
followed by a discussion of imaging findings in healthy individuals and then behavioral and imaging findings in schizophrenia.

At the subcortical level, saccades are governed by the basal ganglia, thalamus, superior colliculus, and brainstem reticular formation (Leigh & Kennard, 2004; Leigh & Zee, 1999; Wurtz & Goldberg, 1989). Cortical control of saccades is supported by the frontal eye fields (FEF), supplementary eye fields (SEF), and regions of posterior parietal cortex (PPC), with additional activity in dorsolateral prefrontal (DLPFC) and anterior cingulate cortices (ACC) to support more volitional saccades (e.g. Brown et al., 2006; DeSouza et al., 2003; Ford et al., 2005; Matsuda et al., 2004; McDowell et al., 2002).

Understanding of the neural correlates of saccadic eye movements in non-patient samples has advanced via the use of non-invasive brain imaging technology including functional magnetic resonance imaging (fMRI; See Appendix). Of particular importance to the present investigation are studies of antisaccade eye movements. Greater activation in basic saccade circuitry (FEF, SEF, PPC, and subcortical structures) during antisaccades compared to prosaccades has been consistently reported in the literature (e.g. McDowell et al., 2008).

In addition to increased activation in basic saccade circuitry during antisaccades, other regions are recruited to support requisite higher-level cognitive demands. Successful antisaccade performance requires inhibition of a prepotent behavioral response, a function that has long been associated with DLPFC (Goldman-Rakic, 1987). Though not an ocular motor area per se, DLPFC is involved in various decisional processes that govern ocular motor behavior, including inhibition of unwanted reflexive saccades via direct communication with the superior colliculus (Pierrot-Deseilligny et al., 2004). While lesions to DLPFC spare visually-guided saccade performance (Pierrot-Deseilligny et al., 1991), they result in a markedly increased percentage of
errors on the antisaccade task (Pierrot-Deseilligny et al., 1991, 2003). The putative role of DLPFC in the antisaccade task, but not the prosaccade task, is further supported by human neuroimaging studies that show greater blood oxygen level dependent (BOLD; See Appendix) activation in DLPFC during antisaccades compared to prosaccades (DeSouza et al., 2003; Matsuda et al., 2004; McDowell et al., 2002; Muri et al., 1998; Sweeney et al., 1996). Using an event-related fMRI paradigm, DeSouza et al. (2003) found that right DLPFC showed significantly greater activity during the instruction phase prior to antisaccades than during the same period prior to prosaccades. This increase in activity may reflect top-down control signals that serve to inhibit the reflexive saccade. Another event-related fMRI study by Ford et al. (2005) demonstrated that this preparatory activity in DLPFC was specific to correct antisaccade trials.

It is of note that not all studies have observed increased DLPFC activation during antisaccades (Kimmig et al., 2001; O’Driscoll et al., 1995; Paus et al., 1993; Raemaekers et al., 2002, 2006a, 2006b). That some studies fail to report significant activity may be a function of task context (Dyckman et al., 2007). Using fMRI to investigate brain activation supporting prosaccades and antisaccades when performed separately as well as within the same run, Dyckman et al. (2007) found increased activation in DLPFC during the antisaccade-alone run only. These findings suggest the possibility that the increased demands of the mixed prosaccade-antisaccade run may have necessitated tonic activity in DLPFC across all blocks.

Another region that is implicated in antisaccades is anterior cingulate cortex (ACC). Numerous studies in the cognitive psychology literature suggest ACC is involved in general conflict monitoring (e.g. MacDonald et al., 2000; Miller & Cohen, 2001) and also in signaling the likelihood of an error (e.g. Brown & Braver, 2005). As the antisaccade task presumably
requires both of these processes, it is not surprising that several studies have observed ACC activation during antisaccades (Brown et al., 2006; Doricchi et al., 1997; Gaymard et al., 1998; Matsuda et al., 2004) and that circumscribed lesions to ACC have been shown to produce impairments in antisaccade performance (Milea et al., 2003). The specific role of ACC is further characterized by Ford et al. (2005). In addition to finding increased ACC activation on anti-compared to pro-trials, examination of separate epochs of saccade trials revealed that ACC activation was greater for correct antisaccades compared to incorrect antisaccades during the preparatory period prior to stimulus onset. These data support the role of ACC in top-down regulation of behavior. ACC activation during the response period, conversely, was greater for incorrect antisaccades, suggesting the putative role in error detection.

Behavioral and Neuroimaging Findings in Schizophrenia

Numerous reports have examined saccadic performance in schizophrenia (see Curtis et al., 2001; Everling & Fischer, 1998; Hutton & Ettinger, 2006; McDowell et al., 1999). Laboratory studies of clinically stable schizophrenia patients performing visually-guided saccades have demonstrated comparable accuracy and latencies between patients and healthy controls. These findings have also been observed in several studies of untreated first-episode schizophrenia patients (Broerse et al., 2002; Hutton et al., 1998; Müller et al., 1999; Straube et al., 1999; Sweeney et al., 1997).

Despite intact performance on visually-guided saccades, a consistent finding in schizophrenia is increased error rates on the antisaccade task (Calkins et al., 2003; Curtis et al., 2001; Ettinger et al., 2004, 2006; Karoumi et al., 2001; Katsanis et al., 1997; McDowell et al., 1999; Radant et al., 2007). This apparent inability to inhibit the prepotent saccade, however, cannot be attributed to a failure to understand task instructions as patients generate corrective
saccades on the majority of trials. Biological relatives of schizophrenia patients also make an increased proportion of antisaccade errors, compared to healthy controls, suggesting that the impairment is not due to medication effects or manifestation of the illness (e.g. Camchong et al., 2008; Clementz et al., 1994; Curtis et al., 2001; Ettinger et al., 2004; Katsanis et al., 1997; McDowell et al., 1999).

Studies using functional neuroimaging have assessed saccade circuitry dysfunction in schizophrenia. The extent to which patients have intact versus disrupted reflexive saccade circuitry is not entirely known. While some studies report that the overall pattern of activation during reflexive saccade generation in schizophrenics is comparable to healthy controls (McDowell et al, 2002), other reports have observed reduced saccade-related activity in medicated (Raemaekers et al., 2002) and un-medicated, first-episode (Keedy et al., 2006) schizophrenia patients.

Several studies have shown that patients show dysfunction in antisaccade-related neurocircuitry. Patients have been shown to have decreased activation in frontal and supplementary eye fields during antisaccades (Camchong et al., 2008) as well as decreased activation in DLPFC (Camchong et al., 2008; Keedy et al., 2006; McDowell et al., 2002; but see Raemaekers et al, 2002). The lack of significant differences in DLPFC in Raemaekers et al. is likely attributed to contextual effects from the use of a mixed prosaccade-antisaccade design (see above). Whereas healthy controls show significant activation of basal ganglia (i.e. the striatum) during antisaccades, this activation has been reported to be absent in patients (Raemaekers et al., 2002). Taken together, these findings suggest that schizophrenia is characterized by dysfunction in one or more nodes in basal ganglia-thalamocortical circuitry (Camchong et al., 2006; Raemaekers et al., 2002).
Limitations of Previous Research

That previous investigations of saccadic performance in schizophrenia have made considerable contributions to understanding this complex disorder is clear. However, these studies were hindered by several important limitations. First, most studies of group differences in neural activity associated with antisaccade performance in schizophrenia compare patients to a sample of healthy subjects, most of whom have excellent antisaccade performance. Another complication in the previous literature is differences in medication status within patient samples. A series of studies have demonstrated that treatment with antipsychotic medication can significantly alter saccadic behavior in schizophrenic patients (for review, see Reilly et al., 2008). Antipsychotics have been shown to significantly increase prosaccade latencies and reduce antisaccade latencies in patients. Antisaccade error rate, however, appears to be unaffected by antipsychotic treatment. Antipsychotic medication has also been shown to impact brain activation observed with fMRI. In one such study, antipsychotic treatment was found to significantly ameliorate pretreatment abnormalities in FEF, PEF, and cerebellum (Keedy et al., 2006). Also of note, antipsychotic medication also significantly reduced function in several regions, including striatum, thalamus, DLPFC, and ACC (Keedy et al., 2006). This raises the possibility that previously-reported frontostriatal abnormalities in schizophrenia may be the consequence of deleterious effects of antipsychotic treatment.

An alternative that circumvents these issues is to examine saccadic performance in non-patient, at-risk samples. Such studies often employ one or more clinical questionnaires to examine saccadic performance in subsets of healthy participants who endorse a high number of odd and unusual (i.e. schizotypyal) experiences (e.g. Ettinger et al., 2005; Gooding et al., 1999, 2005; Holahan et al., 2005; O’Driscoll et al., 1998). These studies avoid medication confounds
by investigating schizophrenia-like symptoms in a non-medicated, healthy sample. A consistent finding in these studies is that healthy participants who score high on self-report questionnaires assessing these schizotypal traits make an increased proportion of errors on the antisaccade task, compared to their non-schizotypal peers.

A variant of the psychometric approach is to classify participants based on behavioral performance on one or more laboratory tasks. A sample with behavioral performance that is better matched to schizophrenia may make a more appropriate comparison group for future studies. This method was employed in a previous study by McDowell and colleagues (2003). A large sample of healthy young subjects was pre-screened using a variant of the antisaccade task. While the mean error rate for normal adults is approximately 20% (Hutton & Ettinger, 2006), a subset of participants in the McDowell study made considerably more errors and were thus classified as a poor performer group. FMRI data acquired from a sample of 12 good (mean=8% errors) and 12 poor (mean=45% errors) performers revealed AS-related activation in basic saccade circuitry that did not differ between groups. Moreover, increased activation in DLPFC was observed in both good and poor performers.

Further investigation of these findings in another large sample of undergraduate students is needed. As such, the present study sought to identify a subset of healthy undergraduate students who make a large proportion of antisaccade errors and to compare saccadic performance and brain activation patterns in these individuals to that of a separate group of undergraduates who perform well on the antisaccade task. Participants who were identified as consistently good and poor performers across two behavioral testing sessions performed saccade tasks during an fMRI scan. Potential implications of this study are twofold. First, examining the neural correlates of poor saccadic performance in individuals with no known neurological or psychopathological
conditions may further characterize the role of cortical control centers in volitional saccade performance. Whether healthy individuals show response inhibition problems that mirror those seen in schizophrenia will show similar dysfunction in prefrontal cortex or basal ganglia remains unknown. Second, these findings may support the utility of using a subset of healthy undergraduates as a more time- and cost-effective comparison group in future behavioral and neuroimaging studies of schizophrenia.

Hypotheses

In the behavioral data, the following differences between good and poor performers were predicted. As poor performers are to be selected based on antisaccade performance, these individuals are expected to make significantly more errors on the antisaccade task, but not to differ from their good-performing counterparts on the prosaccade task. Good and poor performers are expected to have comparable saccade latencies on the pro- and antisaccade task.

In the imaging data, saccade generation will be associated with significant activation in the neural network described above (FEF, SEF, PPC, thalamus, and basal ganglia). Increased DLPFC activation during antisaccades is expected to be observed solely in the good-performing group.
CHAPTER 2

METHODS

Participants

Participants were recruited through the undergraduate psychology research pool. Thirteen good performers (M age = 19.2 years, SE = 0.4, 46% female) and thirteen poor performers (M age = 19.5 years, SE = 0.3, 69% female) were drawn from a larger sample of undergraduate students (N=296, M age = 19.3 years, SE = 0.1; 61% female). All participants were right-handed, in good physical health, and free of history of psychiatric illness or severe head trauma. Participants were screened for contraindications for fMRI imaging. After explanation of study procedures, participants provided informed consent and were given course credit or monetary payment for their time. This study was approved by the University of Georgia Institutional Review Board (#2007-10178-5).

Procedure

Behavioral Sessions

Good and poor performers were selected based on performance during two separate testing sessions, spaced approximately 1-2 weeks apart. During the first session, information about participant demographics and medical history was obtained via an interview with a trained research assistant. Intellectual ability was assessed using the vocabulary and spatial reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Participants also completed the Schizotypal Personality Questionnaire (SPQ; Raine, 1991).
The initial testing session also consisted of an eye movement recording session (consisting of three saccade tasks described below) and an interview with a trained research assistant. Good and poor performers, corresponding to the upper and lower 33% of the antisaccade percentage correct distribution (Figure 2.1), were invited back for a second testing session. Cutoff scores for good and poor performers were 80% and 65% correct, respectively. The second testing session consisted of an eye movement recording session that was identical to the first session.

Eye movements were recorded during the screening sessions using an Eye Trak model 310 eye movement monitor and infrared sensors mounted onto a headband (Applied Science Laboratories, Waltham, Massachusetts, USA). Subjects were seated in front of a color flat-screen monitor in a quiet, darkened room. A chin rest was used to minimize participant head movement and to maintain a constant viewing distance (70 cm) from the screen during the tasks. Eye movement recordings were digitized at 500 Hz and displayed on a computer monitor to allow for continuous monitoring of performance by the experimenter.

**FMRI Session**

FMRI imaging was conducted at the UGA Bio-Imaging Research Center (BIRC) on a 3.0T General Electric 16-channel Signa HDx system. Prior to entering the scanner, participants were reminded of task instructions and were screened by a trained MRI technologist. During imaging, participants lay in a supine position on the gurney and their heads were stabilized using foam padding and a forehead strap. Participants were given earplugs to protect against scanner noise.

Eye movements were recorded with MRI compatible equipment (Meyetrack, SensoMotoric Instruments, Inc., Berlin, Germany). A dual mirror box was placed 16 mm above
and in front of the participant’s eyes. One of the mirrors allowed the participant to view a projection screen placed near his feet. The second mirror projected the image of the participant’s right eye to an infrared camera placed at the back of the magnet bore. The eye was illuminated via an infrared light, and the video signal was displayed on a computer monitor so performance could be monitored and recorded for later analysis. Eye movement recordings were digitized at 60 Hz. Stimuli were rear-projected onto a screen positioned 174 cm from participant’s nasion using an LCD projector (NEC Viewtechnology, Tokyo, Japan). Stimulus presentation was controlled by programs written with Presentation software (Neurobehavioral Systems, Albany, California).

Two localizer images were taken at the beginning of the session to ensure optimal brain coverage for each participant. Three functional runs each consisted of 33 contiguous axial-oblique, gradient-recalled echo-planar images (3.44 x 3.44 x 4 mm, TR=2000ms, TE=30ms, flip angle=90 degrees, scan time = 4 min 54 sec). Oblique slice prescription was achieved by aligning the slices to the superior margin of the anterior commissure and the inferior margin of the posterior commissure. Brain coverage for functional runs was defined by placing the most superior slice tangent to the highest point of the somatosensory cortex. Each functional run began with four dummy samples (which were not included in subsequent data analysis) to allow for magnetic field stabilization. Finally, a high-resolution structural image was obtained (SPGR – protocol: axial, .9375 x .9375 x 1.2 mm, 150 slices, TR=7.8ms, TE=3ms, flip angle=20 degrees, scan time = 6 min 20 sec).

**Stimuli**

Participants completed three conditions in a blocked design (Figure 2.2): Prosaccade vs. fixation (fix-pro), antisaccade vs. fixation (fix-anti), and antisaccade vs. prosaccade (pro-anti).
For the fix-pro and fix-anti runs (hereafter referred to as blocked runs), 7 blocks of fixation (22 sec) alternated with 6 blocks of saccade trials (22sec, 8 trials per block, 48 trials total). The pro-anti run (hereafter referred to as the mixed run) consisted of alternating blocks of prosaccades (22sec, 7 blocks, 56 trials total) and antisaccades (22sec, 6 blocks, 48 trials total). Order of trials and conditions was counterbalanced across participants. On prosaccade trials, participants were instructed to move their eyes to the location of the stimulus as quickly and accurately as possible. On antisaccade trials, participants were instructed to not look at the stimulus and to move their eyes to the mirror image location (opposite direction, same distance from center) as quickly and accurately as possible.

During the fixation block, participants were instructed to fixate on a centrally presented pink dot (1° diameter) for its duration. On saccade trials, a 1° dot was presented at central fixation for 1600ms. The center stimulus was extinguished, and 200ms later (gap), the dot reappeared at ±5° or 10° from fixation in the horizontal plane for 950ms. Trial type was indicated by dot color, with yellow or blue dots signifying pro- or antisaccade trials, respectively.

The gap version of the saccade tasks was selected to produce a greater distribution of percentage correct. Since healthy participants make a larger number of errors with a gap antisaccade paradigm (Fischer et al., 2000; McDowell and Clementz, 1997), using this version facilitated identification of a larger sample of poor performers.

**Data Analysis**

**Behavioral Analyses**

Eye movements recorded during the two screening sessions and in the scanner were scored according to previously published methods (Dyckman and McDowell, 2005) using programs written in Matlab (The Mathworks Inc., Natick, Massachusetts). For each trial, eye
position and eye movement velocity were plotted simultaneously. Trials with blinks near stimulus onset and trials with no saccades were eliminated. Eye movements that began within 80ms of peripheral cue onset were excluded because it is unlikely that such movements were visually-guided. Saccades were scored for correct or incorrect direction, latency, and gain (initial saccade amplitude / target amplitude; 1.0 indicates perfect accuracy). Saccade onset (latency) was defined as the time point at which the eye velocity exceeded 20 degrees of visual angle per second. As participants frequently generate an initial saccade followed by subsequent saccades that serve to correct minor amplitude inaccuracies, separate indices of saccade gain were calculated for initial and final eye positions. For error trials, whether or not the participant made a correction saccade was also scored. Percentage correct was calculated by dividing the number of correct trials in each run by the number of useable trials for that run. Average saccade latencies and gain for correct and error trials were also calculated in a similar fashion.

Eye movement data collected during the fMRI test sessions were analyzed using a series of separate repeated measures ANOVAs in SPSS (Chicago, IL). Percentage correct was analyzed using a 2x2 ANOVAs (Between subjects factor: group [good/ poor]; Within subjects factor: task [pro/anti]). Saccade latencies were examined using a 3x2 ANOVA (Between subjects factor: group; Within subjects factor: trial type [correct prosaccade/correct antisaccade/error antisaccade]. Saccade gain was examined using a 2x2x2 ANOVA (Between subjects factor: group; Within subjects factors: task [pro/anti], gain_type [initial/final]). Finally, effect of task context was examined by entering run type [blocked/mixed] as an additional within subjects factor in the above models (Dyckman et al., 2007).
The relationship between saccade latency and percent correct across all participants was also investigated. Since the percent correct variable was non-continuous (i.e. consisting of dichotomized samples of good and poor performers), point-biserial correlations were employed.

**FMRI Analyses**

Image processing and analyses were conducted with the Analysis of Functional Neuroimages (AFNI; Cox, 1996) software package with methods similar to those previously published (Camchong et al., 2006, 2008; Dyckman et al., 2007). Three dimensional datasets were created from individual image files. For each functional run, images were corrected for slice-dependent time shifts and registered to an ideal base volume to correct for minor head movement. The ideal base volume was defined for each dataset per participant by selecting the median volume of the largest window of time points with the lowest concentration of outlier voxels. Obliquity was removed from the functional datasets using the de-oblique command in AFNI program 3dWarp. Spikes in voxel-wise time series were removed with AFNI program 3dDespike. Voxel-wise percent signal change was then calculated by dividing the signal at each voxel by the mean signal intensity across the entire dataset and multiplying the result by 100. Percent change in BOLD signal from baseline was calculated for each voxel at each of the time points.

A hybrid independent components analysis (ICA) was then performed similar to the approach developed by McKeown (2000) and implemented in Dyckman et al. (2007). This procedure used ICA to derive a set of task-related data-driven regressors that can be used as a reference function in a GLM analysis (McKeown, 2000). An average dataset for each run was created. As noted in Dyckman et al. (2007), averaging across participants reduces computational load, and still accurately estimates associated time courses. The three averaged datasets (one for
each run) were concatenated in space, and Probabilistic ICA (PICA) was performed using MELODIC (Beckmann & Smith, 2004). PICA yielded 38 spatially independent components, the first two of which had time courses with the same frequency as the behavioral paradigm (Figure 2.3).

For each participant, for each run, percent signal change across time was correlated with the first two PICA components, while 27 of the remaining components were used as artifact and/or motion regressors. The artifact components were chosen based on visual inspection of the spatial distribution and the peak frequency of the components (Dyckman et al., 2007).

The resulting datasets for each participant were smoothed using a full width, half-maximum (FWHM) Gaussian filter (4 mm) to account for individual variations in anatomy. Anatomical and functional volumes were transformed into standardized space (based on the Talairach and Tournoux Atlas, 1988) and resampled to 4 x 4 x 4 mm resolution.

To display volitional saccade-related BOLD signal change, data from all participants across all runs were submitted to a voxel-by-voxel, one-sample t test. To protect against false positive, a threshold/cluster method derived from Monte-Carlo simulations (accounting for the 4 mm FWHM Gaussian filter and with a connectivity radius of 5.7 mm) was applied to the t maps (Ward, 1997). On the basis of these simulations, a familywise alpha of .05 was preserved with an *a priori* voxelwise probability of 0.025 and three-dimensional clusters with a minimum volume of 1152 µL (18 or more voxels).

Differences in BOLD activation between groups were examined in a region of interest (ROI) analysis. *A priori* functional ROIs were defined based on regions that showed significant saccade-related activation in a previous large sample fMRI study of healthy undergraduates (Dyckman et al., 2007). There was considerable overlap between activation in the present study
and ROIs in Dyckman et al. (2007), with the exception of middle occipital gyrus (MOG). In this case, significant MOG activation was observed in Dyckman et al. (2007) but not in the present study. The following ROIs were examined: SEF, lateral and medial FEF, DLPFC, ACC, inferior frontal gyrus (IFG), inferior parietal lobule (IPL), precuneus, cuneus, striatum, and thalamus. For each ROI, a sphere (radius 8 mm) was positioned at the center of mass of each ROI (Table 2.1). Mean percent signal changes for each run were calculated for each ROI for each individual, and submitted to an independent samples $t$ test to compare BOLD activation between good and poor groups. Finally, the relationship between antisaccade percent correct and BOLD activation was investigated across all participants using point-biserial correlations.
CHAPTER 3

RESULTS

Demographic Data

Demographic data are shown in Table 3.1. Good and poor performers did not significantly differ on any demographic measure, including age [t(24) = 0.864, p = 0.396] or estimated IQ as assessed by the WASI [Vocabulary, t(24) = 1.316, p = 0.201; Spatial Reasoning, t(24) = -1.782, p = 0.087]. Groups also did not differ on the total number of items endorsed on the SPQ [t(24) = 0.207, p = 0.836].

Eye Movement Data

Effects of Target Direction, Amplitude, and Task Context

Mean percentage correct, latency, and gain of PS or AS trials did not significantly differ as a function of target direction (left vs. right hemifield) or amplitude (5 vs 10 degrees; data not shown). Saccade performance also did not significantly differ between blocked and mixed runs (Table 3.2). Consequently, pro- and antisaccade trials were collapsed across target direction, amplitude, and run type.

Percent Correct

Percentage of correct pro- and antisaccades by group for the fMRI session is shown in Figure 3.1. There were main effects of task [F(1,24) = 104.745, p < 0.001] and group [F(1,24) = 66.065, p < 0.001] as well as a significant task X group interaction [F(1,24) = 35.864]. Poor performers made significantly more errors across both trial types, compared to good performers.
While both groups made more errors on the anti- compared to the prosaccade task, this effect was larger in poor performers.

Latency

Latencies for correct prosaccades, correct antisaccades, and error antisaccades are shown in Figure 3.2. There were main effects of trial type \([F(2,48) = 75.717, p < 0.001]\) and group \([F(1,24) = 7.132, p = 0.013]\). The trial type X group interaction was not significant. Pairwise comparisons indicated poor performers had faster latencies on prosaccades and error antisaccades, but correct antisaccade latencies did not significantly differ between groups. Independent samples \(t\) tests, collapsed across group, showed that latencies of correct antisaccades were significantly longer than both prosaccades and error antisaccades while the latter two did not significantly differ.

Relationship between Saccade Latency and Percent Correct

Point-biserial correlations revealed significant positive associations between antisaccade percent correct and both prosaccade latency \((r = 0.699, p < 0.001)\) and antisaccade latency \((r = 0.420, p = 0.032)\). Thus, participants who tended to respond faster across both saccade types were more prone to commit errors on the antisaccade task.

Gain

Saccade gain on pro- and antisaccade trials is shown in Figure 3.3. The ANOVA revealed significant main effects of gain_type \([F(1,24) = 4.353, p = 0.048]\), task \([F(1,24) = 11.564, p = 0.002]\), and group \([F(1,24) = 6.415, p = 0.018]\). There was also a significant task X group interaction \([F(1,24) = 5.188, p = 0.032]\). Gain type did not significantly interact with any other variables. These results indicate that across both groups, gain of the initial saccade was significantly reduced compared to gain of the final position. All participants also significantly
undershot the target on antisaccades, compared to prosaccades, and this effect was more pronounced in good performers.

*Practice Effects*

Since both behavioral performance and saccade-related brain activation may change as a result of practice (e.g. Dyckman & McDowell, 2005; Dyckman, 2007), change in percentage of correct saccades across the three testing sessions was assessed. The extent to which performance on pro- and antisaccade trials changed across multiple testing sessions is shown in Figure 3.4. A time X task X group ANOVA revealed main effects of time \([F(2,48) = 5.221, p = 0.009]\), task \([F(1,24) = 242.366, p < 0.001]\), and group \([F(1,24) = 113.339, p < 0.001]\). A significant task X time interaction \([F(2,48) = 14.546, p < 0.001]\) indicated that antisaccade performance improved to a greater extent than prosaccade performance. A significant three-way time X task X group interaction was also found \([F(2,48) = 10.064, p < 0.001]\), which is attributed to the significant increase in antisaccade performance and decrease in prosaccade performance that was seen in the poor performer group.

*FMRI Data*

*Saccade-Related Activity*

The clustered one sample \(t\) map collapsed across tasks and groups revealed significant BOLD signal activity in well-characterized saccade circuitry (Figure 3.5). All groups showed increased activation in cortical and subcortical regions known to support saccade performance, including: SEF, FEF, regions of posterior parietal cortex, visual cortex, basal ganglia, and thalamus. Antisaccade performance was associated with recruitment of additional control regions (described below).
Differences between Good and Poor Performers

Prosaccades vs. Fixation

Despite the significant difference in prosaccade percent correct between groups, the pattern of BOLD signal increases associated with prosaccade performance did not significantly differ between good and poor performers. ROI analyses revealed comparable percent signal changes in good and poor performers for each of the ROIs investigated.

Antisaccades vs. Fixation

Clustered $t$ maps showing significant BOLD signal increases during the fix-anti run for good and poor performers are shown in Figure 3.6. Both groups showed increased BOLD signal in the network supporting saccades though activation appeared to be attenuated in poor performers. A between-groups $t$-test collapsed across all ROIs did not a significant difference in overall activation [$t(24) = 0.107, p = 0.916]$. Comparisons of individual ROIs also revealed no significant differences between groups in basic saccade circuitry (FEF, SEF, regions of posterior parietal cortex, thalamus, or striatum). Activation in bilateral DLPFC or ACC also did not significantly differ between groups. Significant between-groups differences were observed in right IFG, with poor performers showing decreased BOLD signal change relative to good performers (Figure 3.7).

To investigate other potential loci of significant differences outside the $a$ priori ROIs, group data was submitted to a voxel-wise random effects $t$ test. This comparison revealed two clusters of greater activation in good performers: left superior frontal gyrus (near Brodmann area (BA) 8; Figure 3.8) and a region in the posterior portion of BA 24 (Figure 3.9).
Prosaccades vs. Antisaccades

When prosaccades and antisaccades were performed in the same run, good and poor performers showed statistically significant differences in a number of ROIs, with poor performers showing decreased signal in all cases (Figure 3.10). Similar to the findings in the fix-anti run, poor performers showed decreased BOLD signal change relative to good performers in IFG and BA 24. Poor performers also showed significantly lower signal in IPL.

Relationship between Antisaccade Performance and FMRI Activation

The association between antisaccade percent correct and fMRI activation was examined using point-biserial correlations. Across all participants, increased BOLD signal in SFG (BA 8) during the fix-anti run was significantly associated with better antisaccade performance \([r = 0.47, p = 0.018]\). Increased activation in right IFG during the fix-anti run also showed a trend-level association with antisaccade performance \([r = 0.34, p = 0.099]\). Antisaccade performance was not significantly associated with BOLD signal in any other ROIs examined.
CHAPTER 4
DISCUSSION

The present study investigated whether a sample of healthy young adults who consistently perform poorly on the antisaccade task (indicated by a large proportion of inhibitory errors) show neuronal abnormalities in brain circuitry supporting saccadic eye movements. A subset of undergraduate students who performed well (>80% correct) or poorly (<65% correct) across two separate eye movement recording sessions performed eye tasks during a functional MRI scan. It was expected that good and poor performers would not significantly differ on prosaccade eye movements, neither in behavior nor brain activation, but that increased antisaccade errors in poor performers would be associated with decreased activation in DLPFC. In this section, behavioral results will be summarized first, followed by discussion of the main imaging findings. Finally, a general discussion will draw upon theories of antisaccade performance to explain differences between good and poor performers.

Behavioral Findings

Poor performers showed marked differences in saccadic performance, compared to their good-performing peers. As anticipated, poor performers committed significantly more direction errors on the antisaccade task, and contrary to predictions, also made more errors on the prosaccade task during the fMRI scan. That seemingly high error rate in poor performers can be attributed to either incomplete understanding of task instructions or a lack of motivation is unlikely since all participants generated corrective saccades on the majority of error trials. Saccade latencies across all trial types were also faster in poor performers. Across all
participants, faster saccade latencies on both pro- and antisaccade trials were significantly associated with decreased antisaccade percent correct. Finally spatial accuracy of prosaccades was significantly hypometric compared to antisaccades—an effect that was more pronounced in good performers.

**Imaging Findings**

Generation of saccadic eye movements was associated with increased BOLD signal change in regions of frontal and posterior parietal cortices known to support volitional eye movements. These areas included SEF, bilateral medial and lateral FEF, precuneus, cuneus, IPL, thalamus, and striatum. Consistent with predictions of the current study, good and poor performers showed similar activation in basic saccade circuitry. Antisaccade performance was accompanied by robust activation in bilateral DLPFC and ACC for both groups. ROI analysis showed that mean percent signal change did not significantly differ between groups for either of these regions.

The lack of significant differences in DLPFC in activation may be explained by neuroplasticity that occurs across multiple testing sessions (for review, see Kelley & Garavan, 2005). Previous reports have demonstrated that repeated practice of saccade tasks produces significant changes in both behavioral performance and neural activation measured with fMRI (Dyckman & McDowell, 2005; Dyckman, 2007). Specifically, repeated antisaccade practice significantly improves antisaccade percent correct (Dyckman & McDowell, 2005). Dyckman (2007) demonstrated that this improvement was accompanied by a significant decrease in DLPFC activation. Increased PFC activation following practice has also been reported. In a study involving 5-weeks of daily training on a working memory task, Olesen et al., (2004) found
that working memory improvement was associated with a significant increase in middle frontal gyrus (DLPFC).

These data suggest a plausible account for similar DLPFC activation between good and poor performers in the present report. Consistent with the findings of Dyckman (2007), it is possible that during the scan session, the antisaccade task had become more automatic for the good performers, and thus reliance on cognitive control resources in DLPFC may have decreased across the testing sessions. Conversely, the results of Olesen et al. (2004) may explain activation in poor performers. It is possible that in these participants, DLPFC activation actually increased across the sessions. Such an effect is illustrated by Jonides (2004) with an example of a mailroom staffed by inexperienced mail clerks. Over time, the clerks become more familiar with the recipients and mail sorting becomes more efficient and accurate. This change could occur by either increasing the expertise of the existing clerks (thereby reducing the need for as many clerks) or by simply adding additional clerks. Changes in PFC activation in the present study may be explained by similar principles: reduction in neural resources (good performers) vs. increased neural recruitment (poor performers). Whether such a pattern explains the present findings is unknown. Future imaging studies using a pre- and post-practice design could potentially characterize whether saccade training differentially affects good and poor performers.

Antisaccade performance was also associated with increased activation in left superior frontal gyrus (SFG) in the good performer group only. This area was located proximal to BA 8—an area that is thought to contribute to higher-level cognitive functions including working memory (du Boisgueheneuc et al., 2006). Evidence from a study examining working memory performance on an n-back task in patients with a left-lateralized lesion to SFG suggests that this region is recruited when executive demand in working memory increased beyond a certain
threshold (du Boisgueheneuc et al., 2006). In other words, as task complexity and/or difficulty increases, areas of SFG are brought online to support requisite executive control demands. Since cognitive demands during the antisaccade task theoretically exceed those during the simpler prosaccade task, increased SFG activation in the present investigation is consistent with this region’s putative role in executive control. That poor performers failed to significantly activate BA 8 may be indicative of a fundamental working memory deficit in these participants. This possibility is discussed in greater detail below.

Successful antisaccade performance in good performers was also associated with increased BOLD signal change in two areas reported to support behavioral inhibition. The first of these regions—the right IFG—was active only in good performers. The evidence for this region’s role in inhibition of prepotent behavioral responses is diverse and includes data from neuropsychology, monkey neurophysiology, and human neuroimaging (for review, see Aron et al., 2004). Damage to the right IFG in humans produces impairments on response inhibition and set shifting paradigms (Aron et al., 2004). Specifically, the greater damage to unilateral right inferior frontal cortex, but not other regions of left or right PFC predicted inhibitory failures on stop-signal tasks (Aron et al., 2003). These data are further corroborated by the monkey physiology literature, which suggests that a lesion to the monkey homologue of IFG significantly impairs go/no-go performance (Iverson & Mishkin, 1970). The widely documented problems with response inhibition that characterize attention-deficit hyperactivity disorder (ADHD) are also attributed to dysfunction in right IFG, as assessed by structural and functional neuroimaging (c.f. Aron et al., 2004).

The specific role of IFG in the inhibition of unwanted saccades in the antisaccade task is also documented. Profound inhibitory deficits on the antisaccade task following damage to right
IFG have been reported previously (Walker et al., 1998). A patient with a lesion confined largely to right IFG committed reflexive errors on 100% of antisaccade trials, despite having no difficulty in performing an anti-pointing task or correct verbal recall of task instructions. In an fMRI study comparing inhibitory activation across different response modalities, Chikazoe et al. (2007) reported significant BOLD signal increases in IFG during the antisaccade task. Similar IFG activation has also been reported in other studies of antisaccades (Dyckman et al., 2007; Dyckman, 2007). These data, combined with the observed positive relationship between IFG activation and antisaccade performance in the present study, suggest that the right IFG is part of the neural network that supports inhibitory aspects of the antisaccade task.

In addition to significantly greater signal in IFG, good performers also showed a significant cluster of greater activation in BA 24. This activation was specific to the posterior portion of the anterior cingulate cortex, an area known as the cingulate eye field (CEF) (Pierrot-Deseilligny et al., 2004). Compared to other higher cortical areas, considerably less is known about the precise role of the CEF in saccadic eye movement control. Evidence from lesion studies, however, suggests that this region is implicated in control of intentional saccades but not reflexive saccades (Gaymard et al., 1998). One function of CEF could be to prepare frontal ocular motor areas involved in intentional saccade control to act in forthcoming motor behaviors (Pierrot-Deseilligny et al., 2004). Neurons in the CEF also influence neuronal activity in DLPFC (Pierrot-Deseilligny et al., 2004) supporting the role of CEF in suppression of unwanted saccades (Milea et al., 2003).

**Relationship to Previous Findings in Schizophrenia**

A central question of the present study was whether healthy individuals who show inhibitory problems similar to those seen in schizophrenia also show neural abnormalities that
characterize the illness. While error rates of poor performers are consistent with high error rates reported in previous studies of schizophrenia, response latency and saccade gain data are inconsistent with schizophrenia. Poor performers did not show the prolonged saccade latencies. Moreover, poor performers also did not show significantly greater hypometria when compared to good performers. In fact, the present results suggest an opposite effect, with good performers undershooting antisaccade targets to a greater extent than poor performers.

Despite making a high proportion of antisaccade errors, the poor performers in the present study seem to successfully recruit DLPFC—another key difference from common findings in schizophrenia. Two of the other areas identified in this study—BA 8 and CEF—have not been reported in previous fMRI studies of schizophrenia. Dysfunction in IFG, however, is implicated in the pathophysiology of schizophrenia. Compromised white matter integrity in IFG, as assessed by diffusion tensor imaging, predicts greater impulsivity in schizophrenia patients (Hoptman et al., 2004). Moreover, a previous study utilizing fMRI to investigate the neural correlates of antisaccade deficits in schizophrenia patients found that patients failed to significantly activate left IFG during antisaccades when compared to healthy controls (Tu et al., 2006). That Tu et al. (2006) observed significant differences in left IFG whereas the current study implicates the right IFG suggests a potential neural difference between poor performing healthy controls and people with schizophrenia. Future neuroimaging studies directly comparing poor performing healthy individuals and persons with schizophrenia would be informative for understanding the significance of lateralized results in IFG.

**Poor Performance and Models of Antisaccade Function**

Several theories have been proposed to account for the cognitive and neural processes that support antisaccade eye movements. These models of antisaccade function have important
implications for understanding the behavioral and neural differences observed in poor performing participants.

Recent evidence emphasizes a parallel processing account to explain competition between pro- and antisaccade eye movements (Massen, 2004; Munoz & Everling, 2004; Reuter & Kathmann, 2004). This model proposes that at stimulus onset the processes underlying exogenously triggered prosaccades and endogenously initiated antisaccades are in competition with one another (Hutton & Ettinger, 2006). The particular response generated depends on whether activation in the neural systems supporting either eye movement reaches a critical threshold to trigger movement initiation. If the activation supporting antisaccades reaches threshold first, the reflexive prosaccade is suppressed and the correct antisaccade is generated. Successful antisaccade performance, therefore, requires attenuation of neural systems supporting prosaccade generation.

The significant trade-off between response latencies and antisaccade errors observed in this study is consistent with this model. The association between latency and error rate has been reported in previous studies of healthy individuals (Evdokimidis et al., 2002). Of particular relevance to the present study, Harris et al (2006) observed a significant speed-accuracy tradeoff between prosaccade latency and antisaccade error rate in schizophrenia patients. Combined with the present data, this relationship suggests that hyper-responsiveness to visual input (manifested in speeded saccade latencies) may predispose an individual to commit antisaccade errors.

This propensity to commit errors could arise because inhibitory neural commands are less able to suppress reflexive saccades to salient visual targets (Harris et al., 2006). These inhibitory commands are thought to originate, in part, from regions of prefrontal cortex, specifically in DLPFC (Hutton & Ettinger, 2006). The present results are inconsistent with this view since good
and poor performers did not show differences in DLPFC activation. The present findings, however, do support the importance of additional cortical regions in suppressing prosaccades. Successful inhibition of the prepotent prosaccade response in good performers was associated with activation in IFG and CEF. Since poor performers failed to significantly activate these regions, accumulating neural signals driving the prosaccade response reached threshold first resulting in a reflexive prosaccade error.

Another account of antisaccade performance emphasizes cognitive constructs such as working memory and active maintenance of task goals (e.g. Engle, 2000; Kane et al., 2001; Unsworth et al., 2004). This theory posits that correct antisaccade performance relies on active maintenance of task goals in working memory. If the task goal (i.e. *don’t look at the dot, look to the mirror image*) is not actively maintained, then momentary lapses in attention will result in attention being captured by the peripheral cue allowing the prepotent response to guide behavior (Unsworth et al., 2004). If the relevant task instructions are adequately maintained, however, successful inhibition of the reflexive saccade emerges as a direct consequence of activation of the task goal (Hutton & Ettinger, 2006).

Multiple lines of evidence support the active maintenance theory. If healthy participants are asked to perform a concurrent task that requires working memory process, antisaccade error rates increase (Mitchell et al., 2002; Roberts, Hager & Heron, 1994). Previous studies utilizing extreme-groups designs have shown that individual differences in working memory span are associated with antisaccade performance. Low span participants have been shown to commit more errors when compared to high spans (Kane et al., 2001; Unsworth, Schrock & Engle, 2004). Unsworth and colleagues suggest that individual differences in working memory span reflect differences in central executive functioning. Therefore, lower working memory span is
thought to interfere with one’s ability to prevent automatic attentional capture and to suppress irrelevant responses.

Considering the reported relationship between high antisaccade error rates and low working memory span, it is possible that poor performing participants in the current study are akin to the low span subjects in these studies. The observed relationship between increased BOLD activation in BA 8 and better antisaccade performance offers preliminary support for this claim. Active maintenance is thought to rely on PFC circuitry (Kane & Engle, 2002) and inefficient neural processing in BA 8 in poor performers could be a potential neural correlate of hypothetical working memory dysfunction in this group. Since the current study did not collect data on working memory span, these hypotheses are necessarily speculative. The specific relationship between working memory capacity and antisaccade performance in poor performers is a useful area for future research.

Conclusions

An important implication of the present study is the identification a sample of healthy young adults who consistently perform poorly on the antisaccade task. These findings suggest the potential utility of using a sample of poor performing undergraduates as a comparison group in future studies of psychiatric illness. Using undergraduate participants as a comparison group may prove to be a more time and cost effective approach.

Taken together, the behavioral and imaging findings suggest that poor antisaccade performance in healthy undergraduates is associated with dysfunction in several areas known to support working memory and response inhibition. Dissociation of neuronal activity for correct versus error antisaccades, however, was not possible due to methodological limitations of using a blocked design. Future studies utilizing event-related fMRI paradigms may reveal other subtle
differences between good and poor performers. Activation differences between good and poor performers only partly resembled previously reported neuronal abnormalities in schizophrenia. Whether other similarities exist between these groups is an area for future studies that directly compare patient samples to a non-patient sample of healthy undergraduates who were screened based on antisaccade performance.
REFERENCES


APPENDIX A

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique that allows for the investigation of brain changes associated with perceptual, motor and cognitive processes (for an in depth review, see Huettel, Song, & McCarthy, 2009). Increased activity in task-related neural circuits that support these processes are theoretically accompanied by increased blood flow into active brain regions. This influx of oxygenated hemoglobin exceeds the local metabolic demand producing an increased ratio of oxygenated to deoxygenated hemoglobin. Increased concentration of oxygenated blood results in a corresponding increase in magnetic signal, which forms the fundamental basis of the signal measured in fMRI. The primary dependent measure in fMRI—the ‘blood oxygen level dependent (BOLD) signal—is a measure of local hemodynamic changes that are indirectly associated with changes in neural activity.

Of the various experimental designs used in fMRI studies, the blocked design (consisting of alternating blocks of task and baseline conditions) used in the current study boasts the advantage of optimized signal-to-noise ratio (Bandettini & Cox, 2000). Moreover, previous studies using blocked designs have demonstrated the successful use of this method to evaluate whole brain activations associated with basic saccade-related neural substrates (e.g. Camchong et al., 2006; Dyckman et al., 2007; McDowell et al., 2002).
**Figure 1.1 Neural Circuitry of Saccades**
Schematic representation of brain regions involved in saccade generation. Black and red lines indicate excitatory and inhibitory connections, respectively. For connections between the basal ganglia and the superior colliculus and thalamus, the black line indicates that the net excitatory effect of the direct pathway and the red line indicates the net inhibitory effect of the indirect pathway. ACC anterior cingulate cortex; DLPFC dorsolateral prefrontal cortex; FEF frontal eye fields; PPC posterior parietal cortex; PPRF paramedian pontine reticular formation of the brain stem; SC superior colliculus; SEF supplementary eye fields. (Adapted from Dyckman, 2007)
Figure 2.1 Antisaccade Performance of Entire Undergraduate Sample
Distribution of antisaccade percent correct scores for entire sample at time 1 (N=296). Unfilled circles represent individual participants. Dotted lines represent upper and lower 33% cutoff scores. Good performers (blue line) scored above 80% correct; poor performers (red line) scored below 65%.
Figure 2.2 Stimuli and Block Design
Stimuli used for (A) fixation, (B) prosaccades, and (C) antisaccades. The arrow indicates where the participant should be looking at each point in time. The fixation-prosaccade run consisted of alternating blocks of fixation and 8 prosaccade trials. The fixation-antisaccade run consisted of alternating blocks of fixation and 8 antisaccade trials. The prosaccade-antisaccade run consisted of alternating blocks of 8 prosaccades and 8 antisaccades.
Figure 2.3 Stimulus Timing and ICA Components
Plots of stimulus presentation (black line) and task-related ICA components across the length of a run. For the stimulus presentation plot, 1 represents the baseline condition, +1 represents the experimental condition. Component 1 is shown in blue; component 2 is shown in red.
Table 2.1
Talairach Coordinates of the Centers of Mass for ROIs.

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<td>-15</td>
<td>+15</td>
</tr>
</tbody>
</table>

ROI, region of interest; SEF, supplementary eye fields; FEF, frontal eye fields; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; IPL inferior parietal lobule.
Table 3.1  
Participant Demographics

<table>
<thead>
<tr>
<th></th>
<th>Good Performers</th>
<th>Poor Performers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13 (4 M, 9 F)</td>
<td>13 (7 M, 6 F)</td>
</tr>
<tr>
<td>Age</td>
<td>19.2 (S.E. 0.4)</td>
<td>19.5 (S.E. 0.3)</td>
</tr>
<tr>
<td>WASI Vocabulary</td>
<td>60.1 (S.E. 2.1)</td>
<td>63.5 (S.E. 1.5)</td>
</tr>
<tr>
<td>WASI Spatial Reasoning</td>
<td>27.8 (S.E. 0.9)</td>
<td>25.8 (S.E. 0.7)</td>
</tr>
<tr>
<td>SPQ Total</td>
<td>20.5 (S.E. 4.2)</td>
<td>21.7 (S.E. 3.7)</td>
</tr>
</tbody>
</table>
Table 3.2
Saccade Performance by Run Type

<table>
<thead>
<tr>
<th></th>
<th>Good Performers</th>
<th>Poor Performers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percent Correct</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prosaccades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Blocked</em></td>
<td>98.9</td>
<td>91.2</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>97.5</td>
<td>91.7</td>
</tr>
<tr>
<td><strong>Antisaccades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Blocked</em></td>
<td>91.5</td>
<td>60.2</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>88.5</td>
<td>61.5</td>
</tr>
<tr>
<td><strong>Latency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prosaccades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Blocked</em></td>
<td>187.6</td>
<td>160.6</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>192.6</td>
<td>166.9</td>
</tr>
<tr>
<td><strong>Correct Antisaccades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Blocked</em></td>
<td>252.9</td>
<td>246.9</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>256.9</td>
<td>241.5</td>
</tr>
<tr>
<td><strong>Error Antisaccades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Blocked</em></td>
<td>201.3</td>
<td>189.3</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>230.3</td>
<td>181.3</td>
</tr>
<tr>
<td><strong>Gain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prosaccades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Blocked</em></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Antisaccades</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Blocked</em></td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td><em>Mixed</em></td>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Figure 3.1 Percent Correct Saccades – FMRI Session
Distribution of prosaccade (left) and antisaccade (right) percent correct scores during the FMRI scan session. Blue triangles represent individual good performers (N=13); red triangles represent individual poor performers (N=13). Mean (and standard error) percent correct also shown for each distribution (black circles). Poor performers made significantly more errors across both tasks, compared to good performers. While both groups made more errors on the anti- compared to the prosaccade task, this difference was greater in poor performers.
Figure 3.2 Saccade Latencies – FMRI Session
Mean (and standard error) saccade latencies for prosaccades (solid bars), error antisaccades (cross-hatched bars), and correct antisaccades (diagonally-hatched bars) for good (blue bars) and poor (red bars) performers during the FMRI session. Poor performers had significantly faster latencies across all trial types, compared to poor performers.
Figure 3.3 Saccade Gain – FMRI Session
Mean accuracy of the initial saccade (and standard error) during prosaccades (solid bars) and antisaccades (hatched bars) for good (blue bars) and poor (red bars) performers. A score of 1.0 (dotted line) indicates perfect spatial accuracy. Values greater than 1.0 indicate saccades that overshoot the target and values less than 1.0 indicate saccades that undershoot the target. Antisaccades were significantly hypometric compared to prosaccades, and this effect was more pronounced in good performers.
Figure 3.4 Percentage of Correct Saccades Across Testing Sessions
Mean (and standard error) percentage of correct prosaccades (top) and antisaccades (bottom) across testing sessions. Times 1 and 2 occurred in the eye movement laboratory; time 3 was collected during the FMRI scan. In both plots, good performers (blue line) are compared to poor performers (red line).
Figure 3.5 BOLD Activity Associated with Saccades
Axial slices (top left z = 10 through bottom right z = 50, spacing = 4 mm) displaying regions with significant percent signal increase (indicated by the color scale) associated with volitional saccade performance in all groups. This one-sample t map was used to determine regions of interest. The background anatomical image is a structural image from one subject in radiological convention (left hemisphere on the right).
**Figure 3.6 BOLD Activation during Fix-Anti Run**
Axial slices (top left $z = 10$ through bottom right $z = 50$, spacing $= 4$ mm) displaying regions with significant percent signal increase (indicated by the color scale) associated with antisaccades during the fix-anti run in good (left) and poor (right) performer groups. The background anatomical image is a structural image from one subject in radiological convention (left hemisphere on the right). Note that while both groups displayed activation in basic saccade circuitry (see Figure 3.5), good performers showed more robust activation in most regions.
Figure 3.7 Antisaccade-Related BOLD Activity in Right Inferior Frontal Gyrus

a) Axial (top left) and sagittal (bottom left) views displaying significant between-group differences in BOLD signal change during the Fix-Anti run in right inferior frontal gyrus (IFG). Overlay reflects areas of significant differences following a between-groups t test comparing antisaccade-related activation in good vs. poor performers (warm colors indicating greater activation in good performers). Note, crosshair position is same in axial and sagittal views (Talairach x,y,z = 42,30,-6). The background anatomical image is a structural image from one subject in radiological convention (left hemisphere on the right). 
b) Mean percent signal change (and standard error) for IFG as a function of group. Good performers (blue bars); Poor performers (red bars)
Figure 3.8 Antisaccade-Related BOLD Activity in Left Superior Frontal Gyrus

a) Axial (top left) and sagittal (bottom left) views displaying significant between-group differences in BOLD signal change during the Fix-Anti run in left superior frontal gyrus (SFG; BA8). Overlay reflects areas of significant differences following a between-groups $t$ test comparing antisaccade-related activation in good vs. poor performers (warm colors indicating greater activation in good performers). Note, crosshair position is same in axial and sagittal views (Talairach $x,y,z = -19, 41, 43$). The background anatomical image is a structural image from one subject in radiological convention (left hemisphere on the right).

b) Mean percent signal change (and standard error) for BA8 as a function of group. Good performers (blue bars); Poor performers (red bars); BA Brodmann area
Figure 3.9 Antisaccade-Related BOLD Activity in Brodmann Area 24

a) Axial (top left) and sagittal (bottom left) views displaying significant between-group differences in BOLD signal change during the Fix-Anti run in Brodmann area (BA) 24—the putative location of the cingulate eye field. Overlay reflects areas of significant differences following a between-groups t test comparing antisaccade-related activation in good vs. poor performers (warm colors indicating greater activation in good performers). Note, crosshair position is same in axial and sagittal views (Talairach x,y,z = 0,-22,35). The background anatomical image is a structural image from one subject in radiological convention (left hemisphere on the right). b) Mean percent signal change (and standard error) for BA 24 as a function of group. Good performers (blue bars); Poor performers (red bars); BA Brodmann area.
Figure 3.10 Group Differences on Pro-Anti Run
Mean percent signal change (and standard error) within ROIs that showed activation differences between good (blue bars) and poor performers (red bars) on the pro-anti run. Positive values indicate greater activity during the antisaccade blocks. Negative values indicate greater activity during the prosaccade blocks. IFG inferior frontal gyrus; BA Brodmann area; IPL inferior parietal lobule.