NEURAL CORRELATES OF ANTISACCADE AND DELAYED RESPONSE TASK PERFORMANCE IN PARTICIPANTS WITH SCHIZOPHRENIA AND THEIR BIOLOGICAL RELATIVES

by

JAZMIN CAMCHONG

(Under the Direction of Jennifer E. McDowell)

ABSTRACT

Schizophrenia is characterized by problems with inhibition and working memory. For example, people with schizophrenia show abnormalities on antisaccade (AS) and ocular motor delayed response (ODR) tasks. Some of the first degree biological relatives of schizophrenia patients have similar abnormalities. The present study used fMRI with simultaneous eye movement recording to evaluate BOLD signal associated with AS and ODR task performance in three groups: schizophrenia patients, their biological relatives, and normal participants. Analyses revealed the following. First, behavioral results showed that (a) the schizophrenia patients generated significantly more errors than the normal group and (b) the relatives of schizophrenia patients showed intermediate error values which were only significantly different from the normal participants. Second, all subjects showed saccade-related activity in expected basal ganglia-thalamocortical circuitry mediating (a) saccade generation including striatum, lateral frontal eye fields (lFEF), supplementary eye fields (SEF), superior parietal lobule (SPL), cuneus and middle occipital gyrus (MOG), and (b) executive functioning including BA 9 and BA 10 in dorsolateral prefrontal cortex (DLPFC), anterior cingulate (ACG), medial FEF, and insula. Third,

while schizophrenia patients and their relatives showed disruptions in BA 10, ACG, cuneus, MOG and insula, such disruptions observed in the relative group were intermediate. Fourth, schizophrenia patients showed additional disruptions in lFEF and SEF. In sum, the results suggest that the neural substrates underlying poor AS or ODR task performance are disrupted in participants with schizophrenia and their relatives. Results suggest that poor inhibition and working memory performance and its underlying neural substrates may be biological markers of schizophrenia.

INDEX WORDS: Schizophrenia, Relatives, Spatial working memory, Inhibition, Memory saccades, Antisaccades, FMRI

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CHAPTER 1

Introduction

The present study aimed to examine the neural functioning abnormalities mediating executive functioning deficits observed in schizophrenia participants and their relatives. A blocked-fMRI study was conducted to compare neural activity of schizophrenia participants, their first-degree biological relatives (primarily siblings) and community controls while their executive functioning was assessed with volitional saccade tasks requiring inhibition and working memory. This study: (1) reviews characteristic deficits in ocular motor tasks previously observed in schizophrenia participants and their relatives, (2) reviews the neural substrates mediating ocular motor task performance in schizophrenia participants and their relatives as compared with normal controls, (3) reports the methods used to conduct this study, (4) presents results after data collection and analyses, and (6) concludes with a discussion section interpreting the results.

Ocular Motor Behavioral Abnormalities in Schizophrenia Participants

Schizophrenia is characterized by a spectrum of behavioral abnormalities that range from clinical symptoms such as delusions, hallucinations and disorganized thinking (American Psychiatric Association, DSM-IV-TR, 2000) to measurable cognitive problems with inhibition and working memory (Chan et al., 2006; Goldman-Rakic, 1994; Kim et al., 2004; Lencz et al., 2006; Park 1997; Snitz et al., 1999). Inhibition and working memory deficits found in schizophrenia can be evaluated easily and effectively in laboratory settings using ocular motor tasks (Curtis et al., 2001; Ettinger et al., 2003; Park & Holzman, 1992).

Ocular motor tasks have been used to assess performance in schizophrenia participants since the beginning of the 20th century (Diefendorf & Dodge, 1908). Ocular motor tasks are optimal tools used to assess cognitive functioning because they (1) are simple tasks that are easy to understand for clinical and normal populations, (2) can be varied to examine different levels of complexity and components of cognitive functioning (Broerse et al., 2001), (3) have good test-retest reliability as well as internal consistency (Ettinger et al., 2003), and (4) have been extensively used in studies that evaluate neural substrates mediating cognitive performance in human and non-human primates (Everling & DeSouza, 2005; Funahashi et al., 1993; Johnston & Everling, 2006).

Schizophrenia participants have demonstrated normal basic eye movements as well as deficient higher level eye movements. If presented with a task that requires an eye movement towards a newly appearing peripheral cue, schizophrenia participants' performance does not differ from normal controls (Clementz et al., 1994; Ettinger et al., 2006; Smyrnis et al., 2004). Schizophrenia participants' performance, however, is compromised if a task requires higher-level executive functioning such as inhibiting a reflexive eye movement response (Hommer et al. 1991; Fukushima et al., 1990; Reuter & Kathmann, 2004) or maintaining internal representations of information (Everling et al., 1996; Goldman-Rakic, 1994; Park & Holzman 1992). Two saccade tasks that have been widely used for assessing executive functioning in schizophrenia participants are the antisaccade (AS; Fukushima et al., 1990; Hutton & Ettinger, 2006; McDowell & Clementz 1997, Reuter et al., 2004) and the ocular motor delayed response (ODR; Everling et al., 1996; Park, 1997) tasks. Because correct performance during these two tasks requires voluntary eye movements involving higher-level executive functioning, the AS and ODR tasks are both considered volitional saccade tasks.

Both volitional saccade tasks, the AS task and the ODR task, require similar components of higher-level executive functioning. AS and ODR tasks both require common (1) visuo-spatial attention demands (Corbetta, 1998), (2) inhibitory control, (3) working memory, and (4) volitional or voluntary generation of a saccade for correct performance (Broerse et al., 2001; Hutton et al., 2004; McDowell et al., 1999, 2001; Nieman et al., 2000; Reuter & Kathmann, 2004; Ross et al., 2000). These components can be measured in the laboratory by using these two volitional saccade tasks. During AS tasks, participants are presented with a visual cue to the left or right of a central fixation. To correctly perform an AS trial, the participant must inhibit a reflexive saccade towards the cue (inhibition component) and simultaneously generate a saccade to the mirror image (same amplitude). An initial saccade toward the cue constitutes an antisaccade error.

During ODR tasks, participants are instructed to remember the location of a peripherally presented visual cue through a delay period (working memory component) without making anticipatory saccades towards the peripheral cue or its spatial location (inhibition component). The saccade to the remembered spatial location (made after the delay period) is called a memory saccade. An initial saccade towards the cue or the remembered location before the delay period is over constitutes an anticipatory error. Since AS and ODR tasks require similar executive functioning components (inhibition, working memory and volitional saccade generation), and performance during both tasks has been found to be highly correlated (participants who perform poorly during the AS task also perform poorly during the ODR task, McDowell et al., 2001), both tasks can be used together to examine executive functioning deficits characteristic to schizophrenia.

Schizophrenia participants have demonstrated characteristic deficits during both the AS and ODR tasks. Schizophrenia participants' behavioral performance during these saccade tasks is characterized by (1) increased inhibitory errors during AS when participants generate a saccade towards the cue instead of away (Fukushima et al., 1988; Fukushima et al., 1990; Radant et al., 2007; Sereno & Holzman, 1995), (2) increased anticipatory errors during ODR when participants generate a saccade during the cue presentation or delay period (Everling et al., 1996; Fukushima et al., 1990; Hommer et al., 1991; McDowell & Clementz, 1996; Park, 1997; Ross et al., 2000) and (3) increased latency and decreased gain of correct responses in both tasks (Hutton et al., 2001; Everling et al., 1996; McDowell & Clementz, 1996; Park & Holzman, 1992).

Poor volitional saccade performance found in schizophrenia participants may indicate behavioral deficiencies characteristic of individuals at risk of developing the disease. Since poor AS and ODR task performance in schizophrenia has been shown to (1) manifest before onset of illness (Pukrop et al., 2006), (2) be relatively stable across time (Broerse et al. 2001; Gooding et al., 2005; Calkins et al., 2003), (3) be present regardless of the schizophrenia participants' symptomatology (Nkam et al., 2001), (4) be present in medicated and non-medicated schizophrenia participants (Harris et al., 2006), and (5) be present regardless of type of antipsychotic medication used (Broerse et al., 2001), these behavioral deficits are good candidates for biological markers of schizophrenia (Calkins & Iacono, 2000; McDowell et al., 1999). In order to find evidence to support the idea that poor AS and ODR performance may be a biological marker for schizophrenia, this trait needs to also be present in biological relatives of schizophrenia participants (Gottesman & Gould, 2003, 2006). Ocular motor research has found evidence of increased error rate during volitional saccade performance in relatives of schizophrenia participants when compared to normal participants.

Ocular Motor Abnormalities in Relatives of Schizophrenia Participants

The identification of specific markers as characteristic traits of individuals at risk of developing schizophrenia is still ongoing. The identification of the diverse clinical symptoms (DSM, 2000) associated with schizophrenia is not sufficient for identifying individuals at risk of developing schizophrenia. Even though there is strong evidence for the heritability of schizophrenia (McGuffin et al., 1984), a single genetic abnormality has not been identified for the disease. Moreover, the interaction of complex genetics and environmental factors contributing to the disease may vary across schizophrenia participants (Tsuang et al., 1990). Gottesman and Gould (2003) have proposed the need for detecting alternative heritable cognitive traits that are more stable, specific and easier to measure. For a cognitive trait to be labeled as a heritable trait, it must (1) be associated with the illness, (2) be heritable, (3) be independent of the manifestation/onset of the illness, (4) show familial co-segregation with the illness, and (5) be present in the relatives of schizophrenia participants with a higher incidence than in the normal population (Gottesman & Gould, 2003, 2006). The identification of cognitive traits and evaluation of the underlying neural substrates present in schizophrenia participants and their relatives will contribute evidence towards identification of biological markers characteristic of individuals at risk of developing schizophrenia.

Relatives of schizophrenia participants have shown several cognitive deficits similar to those of schizophrenia participants (Heydebrand, 2006). Poor volitional saccade performance, in particular, has been found in relatives of schizophrenia participants (Calkins et al., 2004; Curtis et al., 2001; Levy et al., 2004; Malone & Iacono, 2002; McDowell et al., 1999, 2001; Thaker et al., 2000). Various studies have found that relatives of schizophrenia participants show similar performance deficits seen in those with the illness such as (1) increased inhibitory errors during

AS (Clementz et al., 1994; Curtis et al., 2001; Ettinger et al., 2004, 2006; Karoumi et al., 2001; Katsanis et al., 1997; McDowell et al., 1999; Ross et al., 1998), (2) increased anticipatory errors during ODR (McDowell et al., 2001; Park et al., 1995; Ross et al., 1998) and (3) increased latency and decreased gain of saccades in both tasks when compared to normal controls (Ettinger et al., 2004, 2006; McDowell et al., 2001; Park et al., 1995).

Additional evidence suggesting that relatives of schizophrenia participants show increased dysfunction during volitional saccade performance was observed in a study that recruited participants with different degrees of relatedness to the schizophrenia participants (McDowell et al., 1999). McDowell et al. (1999) conducted a study in which first- and second- degree relatives of schizophrenia patients were recruited to perform volitional saccade tasks. A closer degree of relationship between the relative and the schizophrenia participant was associated with more compromised volitional saccade performance in the relative of the schizophrenia participant (McDowell et al., 1999). This study provided evidence suggesting that executive functioning in the schizophrenia spectrum may show a parametric pattern of dysfunction associated to the genetic loading in relatives of schizophrenia participants. Overall, studies showing poor volitional saccade performance in relatives of schizophrenia participants have shown a general pattern in which relatives of schizophrenia participants generate more errors than normal participants, and fewer errors than schizophrenia participants. The literature on poor volitional saccade performance in relatives of schizophrenia participants, however, is still inconclusive (Brownstein et al., 2003; Levy et al., 2004).

It has been proposed that the degree of observed deficits in relatives of schizophrenia patients may vary depending on the selection criteria of participants (Levy et al., 2004). A meta-analysis conducted by Levy et al. (2004) suggested that relatives of schizophrenia participants show

similar volitional saccade performance to normal participants if similar criteria are used when recruiting participants for both groups. A contemporaneous meta-analysis conducted by Calkins et al. (2004), however, addressed this hypothesis and reported that relatives of schizophrenia participants recruited with the same selection criteria as the normal participants do show increased error rates during volitional saccade performance. Calkins et al. (2004) also found that relatives of schizophrenia participants excluded from the analyses (who did not meet inclusion criteria used for the control group), did not significantly differ in error rates from the relatives of schizophrenia patients included in the analyses. The meta-analysis conducted by Calkins et al. (2004) suggests that rather than being associated with clinical symptoms present in schizophrenia, poor volitional saccade performance observed in relatives of schizophrenia participants is an important piece of biological evidence associated with heritable traits that will indicate genetic vulnerability to the disease (Hutton & Ettinger, 2006).

The evaluation of schizophrenia participants' consistently poor volitional saccade task performance has been a helpful tool to identify behavioral markers associated with the disease (e.g. Clementz et al., 1994; Curtis et al., 2001; Ettinger et al., 2004, 2006; Karoumi et al., 2001; Katsanis et al., 1997; McDowell & Clementz, 1997). To be considered a reliable, heritable behavioral marker of schizophrenia, however, poor volitional saccade performance should also be consistently found in individuals genetically predisposed to the disease such as relatives of schizophrenia participants (Gottesman & Gould, 2003). Relatives of schizophrenia participants, however, have not shown consistent and reliable evidence of poor volitional saccade performance (Brownstein et al., 2003; Levy et al., 2004). Therefore, poor volitional saccade performance may not be a sufficient heritable marker for identifying individuals at risk of

developing schizophrenia. The investigation of such behavioral markers needs to be complemented with the examination of their underlying biological mechanisms.

Biological mechanisms mediating poor executive functioning provide a more sensitive measure for examining the heritable biological markers of schizophrenia. Genetic susceptibility for developing a disease is more directly associated with underlying biological deficits than to observable behavioral deficits. Biological mechanisms underlying poor volitional saccade performance, such as brain morphology (Ettinger et al., 2004; Schulze et al., 2006) and neural activity (Camchong et al., 2006; Keedy et al., 2006; McDowell et al., 2002; Raemaekers et al., 2002, 2006a; Tu et al., 2006), have been used to more intimately investigate biological abnormalities associated with genetic susceptibility for developing schizophrenia. Magnetic resonance imaging (MRI) studies, evaluating the brain morphology of schizophrenia participants and their relatives, have found that poor volitional saccade performance may be associated with structural abnormalities such as larger caudate and smaller premotor volume (Ettinger et al., 2004) as well as smaller prefrontal cortex volume (Schulze et al., 2006). Functional magnetic resonance imaging (fMRI), evaluating neural activity mediating AS and ODR performance in schizophrenia and their relatives, has taken a step further to examine the biological mechanisms underlying poor volitional saccade performance.

Neural Substrates Mediating Volitional Saccades during AS and ODR performance

Because AS and ODR tasks measure overlapping components (visuo-spatial attention, inhibition, working memory, volitional saccade generation), behavioral performance during these two tasks is mediated by an overlapping neural circuitry (Sweeney et al., 2007). Volitional saccades generated during AS and ODR task performance have been shown to be supported by a neural circuitry comprised of both subcortical and cortical regions. The identification and

hypothesized contribution of these regions have been studied using nonhuman primates (Chafee & Goldman-Rakic 2000; Inoue et al., 2004; Johnston & Everling, 2006; Funahashi et al., 1993), as well as certain clinical (Keedy et al., 2006; Pierrot-Deseilligny et al., 2003a, 2003b; Gaymard et al., 1999; Ploner et al., 1999, 2005; Raemaekers et al., 2002; Tu et al., 2006) and normal (Brown et al., 2004, 2006; Curtis et al., 2004; DeSouza et al., 2003; Sweeney et al., 1996) human samples.

Volitional saccade performance during AS and ODR tasks is comprised of two components: (1) a lower level component involved in motor processes such as triggering and generation of saccades and (2) a higher level component involved in executive functioning such as planning, inhibiting, and/or maintaining information. Lesion and neuroimaging studies have tried to identify particular subcortical and cortical regions mediating either one or both of these two components. Regions within the volitional saccade circuitry that primarily (but not exclusively) mediate the motor component of task performance have been identified as: basal ganglia (BG), posterior parietal cortex (PPC), lateral frontal eye fields (lFEF), and supplementary eye fields (SEF; Briand et al., 1999; Boxer et al., 2006; Chan et al., 2005; DeSouza et al., 2003; Ford et al., 2005; Matsuda et al., 2004; McDowell et al., 2002, 2005; Pierrot-Deseilligny et al., 2004; Ploner et al., 1999, 2005). Lesion and neuroimaging studies have also identified regions that primarily (but not exclusively) mediate the executive component of volitional saccade performance such as anterior cingulate gyrus (ACG), medial frontal eye fields (mFEF), SEF, and prefrontal cortex (PFC; Camchong et al., 2006; DeSouza et al., 2003; Ford et al., 2005; Gaymard et al., 1998; Johnston & Everling, 2006; McDowell et al., 2002, 2005; Pierrot-Desseilligny et al., 2003a, 2003b, 2004; Ploner et al., 2005; Sweeney et al., 1996). The subcortical and cortical regions

mediating volitional saccade performance comprise the basal ganglia-thalamocortical circuitry (BGTC; Alexander, 1994; Camchong et al., 2006; Matsuda et al., 2004).

Lesion and neuroimaging studies have suggested that within the BGTC, the prefrontal cortex (PFC) in particular plays a crucial role during correct volitional saccade performance (Ford et al., 2005; Funahashi et al., 1989; Inoue et al., 2004; Milea et al., 2005; Pierrot-Deseilligny et al., 2003a, 2005; Sweeney et al., 1996). Lesions studies have shown that PFC abnormalities result in poor volitional saccade performance characterized by increased error saccades (Pierrot-Deseilligny et al., 2003a, 2005; Ploner et al., 2005) and decreased accuracy of memory saccades (Funahashi et al., 1989). Neuroimaging studies providing optimal temporal information such as event related fMRI, EEG and MEG have found that increased PFC activity prior to saccade generation presumably mediates the inhibition of inappropriate saccades in order to support task-appropriate behavior (Brown et al., 2004; DeSouza et al., 2003; Ford et al., 2005; McDowell et al., 2005).

Neuroimaging studies evaluating clinical populations have also found that PFC plays a crucial role in volitional saccade performance. Participants that show poor volitional saccade performance also show a disruption in PFC characterized by decreased activity in this region (Camchong et al., 2006; Keedy et al., 2006; Luna et al., 2002; McDowell et al.., 2002; Tu et al., 2006). Two particular studies from our group examining the neural correlates mediating volitional saccade performance in schizophrenia participants have shown evidence of the important role of PFC in executive functioning. First, in a blocked fMRI study, McDowell et al. (2002) compared neural activity of 13 normal and 14 schizophrenia participants while they performed basic saccade (look towards appearing cue) and AS tasks. FMRI results showed basic saccade-related signal increase in FEF and SEF for both groups. The schizophrenia participants,

however, showed increased antisaccade-related activity in PFC when compared to the normal participants. This study suggests that although the regions in the circuitry involved during basic saccade performance were unaffected in schizophrenia participants, a PFC disruption seems to affect AS performance in schizophrenia participants. The second blocked fMRI study (Camchong et al., 2006) compared neural activity of 14 schizophrenia and 14 normal participants while they performed fixation and ODR tasks. Eye movement data recorded during imaging showed behavioral abnormalities in schizophrenia participants similar to those previously reported: (1) more trials with anticipatory saccades, (2) memory saccades with longer latencies, and (3) memory saccades of decreased accuracy. FMRI results showed saccade-related signal increase during ODR in the basic saccadic circuitry (SEF, FEF, and PPC) for both groups. The normal, but not the schizophrenia group, demonstrated increased BOLD signal in DLPFC, mFEF, insula, thalamus and basal ganglia. Results from this study suggest that a disruption within the BGTC involving PFC seems to mediate poor ODR performance in the schizophrenia participants.

Evidence from lesion and neuroimaging studies suggests that poor volitional saccade performance should be associated with a disruption of the BGTC circuitry. There are still discrepancies, however, in the specific regions of the volitional saccadic circuitry that mediate poor volitional saccade performance previously observed in schizophrenia participants as well as their relatives. Some studies have proposed a general attenuation in BOLD signal change in all regions comprising the BGTC circuitry in schizophrenia participants (Camchong et al., 2006; Keedy et al., 2006; Tu et al., 2006). Furthermore, while some studies emphasize particular disruptions in PFC (Camchong et al., 2006; McDowell et al., 2002; Keedy et al., 2006; Tu et al., 2006) other studies suggest disruptions in basal ganglia (Raemakers et al., 2002).

Discrepancies in findings may reflect context differences depending on the ocular motor tasks being compared (Dyckman et al., 2007). Since fMRI measures task-related signal change between two conditions, a baseline condition (i.e. fixation or prosaccade) and an experimental condition (i.e. AS or ODR), the magnitude of signal change between the two conditions being compared may depend on the type of baseline chosen. A blocked fMRI study providing optimal spatial resolution and detection power has suggested that increased activity in PFC during volitional saccade performance is contingent on the type of baseline used to contrast with the ocular motor task of interest (Dyckman et al., 2007). If the alternation between the baseline and saccade tasks requires complex processes for response selection due to increased difficulty in maintenance of task instructions (i.e. baseline: look towards cue; experimental task: look away from cue), the percent signal change in PFC between blocks will be most likely unnoticeable (Dyckman et al., 2007). If the alternation between the baseline and saccade tasks, however, is less complex so that executive functioning is primarily needed only during the saccade task (i.e. baseline: central fixation; experimental: look away from cue), the percent signal change in PFC will be better detected (Dyckman et al., 2007). Further research designed to maximize the detection of PFC activity needs to be conducted in order to investigate whether PFC activity mediates differences in executive functioning between schizophrenia and normal participants.

Given that schizophrenia participants and their relatives show similar executive functioning deficits during ocular motor tasks, it is hypothesized that the relatives of schizophrenia participants should also show similar disruptions in the BGTC circuitry. Very few neuroimaging studies have been conducted to examine the neural substrates of volitional saccade performance in relatives of schizophrenia participants. Furthermore, results from this limited number of studies are inconclusive.

Different abnormalities have been found in the BGTC circuitry of relatives of schizophrenia participants. One event-related fMRI study evaluating the neural substrates of executive functioning during an AS task performance, found that unaffected siblings of schizophrenia participants showed decreased activity only in BG when compared to demographic- and performance- matched normal controls (Raemaekers et al., 2006a). Another fMRI ocular motor study evaluating the neural substrates of executive functioning during an ODR task, found that offspring of schizophrenia participants showed decreased activity in DLPFC and PPC when compared to demographic-matched normal controls (Keshavan et al., 2002).

There are various possible reasons why results from the two ocular motor studies mentioned above may differ. Factors that may have yielded different results between Raemaekers et al. (2006a) and Keshavan et al. (2002) are: sample size used (16 vs 4 relatives), location and number of scanned slices (24 slices from top of brain down vs. 7 slices superior to the corpus callosum), and different fMRI designs used to identify task-related neural activity (event-related vs. blocked fMRI designs). Results reported by Raemaekers et al. (2006a) had stronger statistical power since they had a sample size of 16 relatives of schizophrenia participants compared to a sample size of 4 in the study conducted by Keshavan et al. (2002). Basal ganglia differences found by Raemaekers et al. (2006a) were not possible for Keshavan et al. (2002) since they scanned volumes only above the corpus callosum. Keshavan et al. (2002) may have found more differences in activation (e.g. DLPFC, PPC) between groups because of the optimized power of blocked designs to detect BOLD signal changes. The advantage of using a blocked design is that it optimizes the detection of areas that show task-related signal changes (Birn et al., 2002). Since the few ocular motor studies conducted to assess executive functioning in relatives of

schizophrenia participants are inconclusive, the following paragraphs review studies that have used other tasks to assess executive functioning.

By using other types of assessment tools besides ocular motor tasks, other FMRI studies have also found BGTC disruptions associated with executive functioning in relatives of schizophrenia participants (Brahmbhatt et al., 2006; Callicott et al., 2003; Karlsgodt et al., 2007; Seidman et al., 2006; Thermenos et al., 2004; Vink et al., 2006). These studies, however, have not been consistent in identifying particular disruptions in the BGTC as well as the nature of this disruption. While most studies have found that relatives of schizophrenia participants show PFC abnormalities associated with executive functioning (Brahmbhatt et al., 2006; Callicott et al., 2003; Karlsgodt et al., 2007; Seidman et al., 2006; Thermenos et al., 2004), it has also been found that relatives of schizophrenia patients have disruptions in basal ganglia associated with executive functioning (Vink et al., 2006). Additionally, results are not consistent within the studies that report PFC abnormalities during task performance in relatives of schizophrenia participants. Some studies have found decreased PFC activity (Brahmbhatt et al., 2006; Karlsgodt et al., 2007), while other studies have found increased PFC activity (Callicott et al., 2003; Seidman et al., 2006; Thermenos et al., 2004) associated with working memory performance in schizophrenia participants and their relatives.

Inconsistent findings during executive functioning assessment may be a result of differences in task demand and difficulty. Evidence for this hypothesis has particularly been shown in an fMRI study comparing the neural correlates mediating executive functioning during an item recognition task (modified Sternberg Item Recognition) with varying levels of working memory loads (Karlsgodt et al., 2007). Participants were required to indicate whether a consonant letter matched a previously presented consonant within a group of 3, 5, 7, or 9 letters. Karlsgodt et al.

(2007) found that schizophrenia participants, their relatives (unaffected twins of schizophrenia participants) and normal participants (healthy pairs of twins) showed interesting patterns of results between behavioral performance and brain activity. Karlsgodt et al. (2007) found a linear relationship between behavioral performance and task-related signal change in PFC that differed between groups. In schizophrenia participants and their relatives good working memory performance was associated with increased PFC activity, while poor working memory performance was associated with decreased PFC activity. In the normal participants good working memory performance was associated with decreased PFC activity, while poor working memory performance was associated with increased PFC activity. These results suggest that there are different mechanisms for recruitment of neural activity between individuals in the schizophrenia spectrum and normal participants during executive functioning performance. Karlsgodt et al. (2007) also found that the magnitude of general brain activity for the relatives of schizophrenia participants was intermediate between schizophrenia participants and healthy control twins (Karlsgodt et al., 2007). This pattern of brain activation during executive functioning was characterized by higher task-related brain activity in the normal participants, lower task-related brain activity in the relatives of schizophrenia participants and lowest task-related brain activity in the schizophrenia participants. This parametric pattern of brain activity across groups is comparable to the parametric pattern of behavioral results during ocular motor tasks reviewed previously (better performance in normal participants, lower performance in relatives of schizophrenia participants and lowest performance in schizophrenia participants during volitional saccade tasks). This parametric pattern of brain activation, however, has not been studied in studies using ocular motor tasks mainly because studies including relatives of schizophrenia patients did not recruit the corresponding schizophrenia participants. Further

research needs to be conducted to identify neural abnormalities underlying executive functioning deficits during ocular motor tasks in schizophrenia participants and their relatives in order to determine possible behavioral and neural abnormalities characteristic to the disease.

The present study was designed to compare the neural substrates mediating executive functioning in schizophrenia participants, their first-degree relatives and normal control groups. This project will add to the schizophrenia literature by (1) using a blocked design to maximize detection of BOLD signal changes in brain regions mediating executive functioning, (2) investigating neural abnormalities mediating volitional saccade tasks in the schizophrenia spectrum, (3) recruiting samples of schizophrenia participants, their first-degree biological relatives, and normal controls, and (4) using both the AS and the ODR tasks as tools to assess similar executive functioning components, (because the main interest of this study is evaluating executive functioning in the schizophrenia participants and their relatives, the AS and ODR tasks will be considered as one measurement of higher-level executive functioning).

The following hypotheses will be tested. First, schizophrenia participants and their relatives will generate increased errors during AS and ODR tasks, as well as response saccades with increased latencies and decreased gains (Ettinger et al., 2006; Karoumi et al., 2001; McDowell et al., 1999, 2001; Ross et al., 1998; Part & Holzman, 1992; Park et al., 1995). Second, schizophrenia participants and their relatives will show a disruption in the basal ganglia-thalamocortical circuitry mediating AS and ODR performance, particularly in DLPFC, FEF, ACC, and/or BG (Camchong et al., 2006; Chan et al., 2005; Desouza et al. 2003; Ford et al., 2005; Keedy et al., 2006; Raemaekers et al., 2006b; Tu et al., 2006).

In sum, this study is important because it is the first fMRI study that will directly compare behavioral and neural functioning between schizophrenia participants, their first-degree relatives,

and a normal group using of two types of volitional saccade tasks. This will be the first study recruiting relatives of schizophrenia participants that will maximize behavioral differences between groups by using two different ocular motor tasks to assess different levels of executive functioning. The evaluation of neural substrates mediating poor volitional saccade performance in schizophrenia participants and their first-degree relatives will provide evidence to address the hypothesis that executive functioning deficits and its underlying neural abnormalities may be good candidates for biological markers of schizophrenia.

CHAPTER 2

Methods

Participants

Fifteen DSM-IV participants diagnosed with schizophrenia (age: M = 39 yrs, SD = 11), 13 of their first-degree biological relatives (age: M = 41 yrs, SD = 15), and 14 normal participants (age: M = 40 yrs, SD = 11) were studied. Relatives and schizophrenia participants were recruited from regional mental health centers and from newspaper and television advertisements. Schizophrenia participants were diagnosed using the Patient Edition of the Structured Clinical Interview for DSM-IV (First et al., 1995). Schizophrenia participants were also screened with Scales for the Assessment of Negative Symptoms (SANS), Scales for the Assessment of Positive Symptoms (SAPS) and Global Assessment Functioning (GAF). Medication information was recorded for schizophrenia participants. Relatives of schizophrenia participants were interviewed with the Non-Patient Edition of the Structured Clinical Interview for DSM-IV-TR (First et al., 1995). Relatives were also screened for schizotypal tendencies with the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) and a series of Scales of Psychosis Proneness (Magical Ideation, Revised Physical Anhedonia, Physical Anhedonia, Revised Social Anhedonia, and Ideation Scales; Chapman & Chapman, 1980). Eighty-five percent (N=11) of the relatives of schizophrenia participants were siblings (one was an offspring, and one was a parent). Eighty-five percent (N=11) of the relatives of schizophrenia participants had no DSM-IV Axis I disorders (two were diagnosed with bipolar disorder). Normal participants were recruited through advertisements placed in the community, as well as newspaper and television

advertisements. Normal participants were selected so that they match the other groups in age and gender.

All participants were right-handed and free of serious physical health problems and absent of known neurological hard signs. Exclusion criteria included loss of consciousness for more than 30 minutes, or a history of severe head trauma or drug abuse. Participants were also screened for contraindications for fMR imaging (e.g. metal in their bodies). All participants provided informed consent as per UGA Institutional Review Board approval (# 10791) and were paid for their time.

FMRI Scanning.

Brain imaging was performed at the Athens Orthopedic Clinic MRI Center using a GE Signa Horizon LX 1.5T MRI scanner (Milwaukee, WI). Immediately prior to entering the scanner, participants were given instructions and shown illustrations of the tasks. During imaging, participants laid in a supine position on the gurney and their heads were stabilized with foam padding and head restraints. Earplugs were used to reduce scanner noise by approximately 30dB. A dual mirror box was placed 16 cm above and in front of the participant's eyes designed to make: (1) stimuli visible to the participant and (2) the participant's eyes visible to an eye-tracking camera for recording eye movements (MeyeTrack LR, SensoMotoric Instruments, Inc., Berlin, Germany). An LCD Projector (NEC Viewtechnology, Ltd., Tokyo, Japan) presented stimuli onto a rear projection screen, which stood approximately 174 cm from participant's nasion. Stimulus presentation was controlled using Presentation software (Neurobehavioral Systems, Albany, CA).

After positioning participants in the scanner, a three-dimensional T1-weighted structural MRI scan with higher-resolution was collected [spoiled gradient-recall (SPGR) protocol: TE=2.8

msec, TR=10.8 msec, flip angle=20°, 2 NEX, matrix=256 x 256, field of view=24 (resulting in an in-plane resolution of 0.97 x 0.97), slice thickness of 1.5 mm, sagittal acquisition, 124 contiguous slices, scan time 5 min 41 secs] for definition of anatomical structures within each brain. Following structural imaging, participants were briefly reminded of the task instructions, and series of T2*-weighted functional images were obtained [axial prescription, spoiled-gradient pulse sequence (SPGR) with a spiral readout pattern in k-space, (matrix=64 x 64, field of view=24 resulting in an in-plane resolution of 3.75 x 3.75, slice thickness=4 mm), TE=40 msec, TR=1912 msec with two interleaves, for an image acquisition time of 3.8 secs; flip angle=77°, 24 supratentorial contiguous slices. For the AS run 81 images were collected for a scan time of 5 min 8 secs. For the ODR run 97 images were collected for a scan time of 6 min 9 secs. The volume of brain coverage for functional scans was defined by placing the most superior scan plane tangent to the highest point of the somatosensory cortex.

Eye Movement Stimuli.

Participants performed two saccade runs in the scanner in a blocked design. Both runs alternated blocks of fixation (see Figure 1A) as a baseline condition (22.5 seconds duration) with blocks of a saccade condition. A change in the geometrical shape around the fixation cross signaled a task change: a square box around the fixation cross signaled the baseline condition and a diamond around the fixation cross signaled a saccade condition. The saccade conditions were either (1) blocks of eight antisaccade (AS) trials (see Figure 1B) during the AS run, or (2) blocks of six ocular motor delayed (ODR) response trials (see Figure 1C) during the ODR run. The order of runs across subjects was counterbalanced to avoid order effects.

Eye movements were recorded using MRI compatible equipment (MeyeTrack LR, SensoMotoric Instruments, Inc., Berlin, Germany) during both saccade runs.

Fixation Block

A cross with a box around it was presented at central fixation. Participants were instructed to fixate on the cross as it remained in the center of the screen (22.5 seconds).

Antisaccade Trial

During an AS trial, participants were instructed to keep their eyes on a centrally presented cross with a diamond around it as long as it was present (1700 msec). The diamond extinguished, and 200 msec later (gap), a 1° gray dot was presented 8° to the left or right of fixation in the horizontal plane for 1250 msec. Participants were instructed to move their eyes as fast as possible to the mirror image location of the cue (opposite side, same amplitude). The gap version of the antisaccade task was selected to avoid a ceiling effect on percentage of correct responses, particularly in the normal control group, which could confound the comparison between groups. Normal controls make a larger number of errors on antisaccade tasks when a gap exists (e.g., Fischer et al., 2000; McDowell & Clementz, 1997).

ODR Trial

During an ODR trial, participants were instructed to keep their eyes on a centrally presented cross with a diamond around it as long as it was present. After 1500 msec of fixation, a 1° gray dot was presented for 100 msec at one of six peripheral locations (4°, 8°, or 12° to the left or right of fixation in the horizontal plane; pseudorandomly selected). Participants were instructed to remember the location of the peripheral cue while keeping their eyes fixated on the central cross. After a delay period of 2500 msec the fixation cross was turned off, signaling the participants to move their eyes to the remembered location as quickly and accurately as possible. Participants had 1300 msec to respond before a one deg star appeared in the correct location (500 msec) to reinforce the accuracy component of the task.

Data Analyses

Behavioral Analyses

Eye movements recorded during task performance in the scanner were analyzed using programs written in Matlab (Mathworks, Natick, Massachusetts) for: (1) the percent error during AS trials and ODR trials ([number of trials with at least one inhibitory or anticipatory saccade/total number of useable trials]*100), (2) the latency of antisaccades and memory saccades (time in milliseconds between fixation offset and the start of the saccade [~90 milliseconds]), and (3) the gain of antisaccades and memory saccades ([initial eye position/cue position]*100; 100% indicates perfect accuracy).

Since previous literature has found that performance during AS and ODR tasks is highly correlated (McDowell et al., 2001), analyses of variance were conducted to look for between-groups differences in (1) percent error, (2) latency of responses and (3) gain of initial and final eye position of responses during AS and ODR tasks combined.

FMRI Analyses

Analyses were conducted using Analysis of Functional NeuroImages (AFNI; Cox, 1996). Three-dimensional datasets were created from individual image files. For each run, all volumes were registered to the middle volume to correct for minor head movement over time. A full width, half-maximum (FWHM) Gaussian filter of 4 mm was applied to each dataset to account for individual variations in anatomy. For each voxel, the percent change in BOLD signal between the baseline (fixation) and experimental (AS and ODR) was calculated for each of the time points.

For each subject, for each run, six factors were entered into a regression model including the experimental and baseline conditions, one linear drift factor, and three motion parameters (i.e.,

roll, pitch, and yaw) in order to evaluate blood oxygenation level-dependent (BOLD) signal change (i.e., "activation"). Anatomical and functional volumes were transformed into Talairach space (Talairach & Tournoux, 1988) and resampled to 4×4×4 mm resolution.

To display AS and ODR-related BOLD signal change, data combined from all participants in all groups 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 4 mm FWHM Gaussian filter and with a connectivity radius of 5.6 mm) were applied to the *t* map (Ward, 2000). Based on these simulations, the family-wise alpha of .05 was preserved with an a priori voxel-wise probability of .025 and three-dimensional clusters with a minimum volume of 1024 μL (16 or more voxels). The resulting averaged, clustered one-sample *t* map was used to identify regions of interest (ROIs) that showed BOLD signal changes associated with AS and ODR performance (compared to zero) for all participants in all groups combined.

ROIs were determined based on BOLD activations observed in the present data, which were consistent with previous fMRI studies of saccadic performance that demonstrate characteristic activations (i.e. Dyckman et al., 2007). For each region of interest (ROI), a sphere (radius 8 mm) was centered at the center of mass of each cluster that showed significant AS and ODR-related signal change in the clustered one-sample *t* map. Mean intensity changes were calculated for each ROI for each individual. For each ROI, a 3 X 2 ANOVA was conducted to look for effects of task (AS, ODR) and effects of group (NP, RL, SZ).

CHAPTER 3

Results

Behavioral Results

Scoreable behavioral data for antisaccade (AS) and ocular motor delayed response (ODR) task performance were available for 98% of participants (14 schizophrenia participants, SZ; 13 relatives of schizophrenia participants, RL; and 14 normal participants, NP). Failure to score one schizophrenia participant's data was due to technical problems associated with insufficient contrast between the pupil and the iris.

A 3 (group: SZ, RL and NP) X 2 (task: AS and ODR) analysis of variance revealed no significant effect of tasks, $F(1,38)=1.236$, $p=0.273$. Percent error values during the AS task and ODR task were significantly correlated in the SZ group ($r=0.68$, $p=0.01$), the RL ($r=0.57$, $p=0.04$) group, and the NP group ($r=0.58$, $p=0.03$). Because performance between AS and ODR tasks error rates did not significantly differ and were significantly correlated, performance data presented hereafter were combined across AS and ODR tasks and are represented as performance during volitional saccade tasks.

Percent Errors. Results showed that there was an overall significant difference in percent errors generated between groups during volitional saccade task performance, $F(2,38)=3.428$, $p=0.043$. Post hoc Tukey tests revealed that the SZ group (M=27.38 % error, SE=5.20) generated significantly more errors than the NP group (M=9.10 % error, SE=5.20, $p=0.045$). The error values for the RL group were intermediate (M=23.54 % error, SE=5.40) and differed significantly only from the normal group ($p=0.045$, see Figure 2).

Latency of Responses. Results showed that the latency of responses did not show an overall significant difference between groups during volitional saccade task performance, $F(2,38)=0.725$, $p=0.491$. There was, however, a tendency for the NP group (M=365.40 msec, SE=25.62) to generate faster responses than the RL group (M=391.96 msec, SE=26.58, p=0.754) and the SZ group (M=408.65 msec, SE=25.62, p=0.464; see Figure 3).

Gain of Responses. The gain (eye position / target position) of initial and final eye position was analyzed separately. Results showed that there was an overall significant difference in the gain of the initial eye position of a response generated during volitional saccade task performance, $F(2,38)=5.194$, $p=0.01$. Post hoc Tukey tests revealed that the initial eye position of responses in the SZ group (M=0.78, SE=0.07) showed significantly less gain than the NP group (M=1.06, SE=0.07; p=0.018) and RL group (M=1.05, SE=0.07; p=0.027; see Figure 4).

There was an overall significant difference in the gain of the final eye position of a response generated during volitional saccade task performance, $F(2,38)=3.652$, $p=0.035$. Post hoc Tukey tests revealed that the final eye position of responses in the SZ group (M=0.86, SE=0.05) tended to show less gain than the NP group (M=0.97, SE=0.05; p=0.199) and showed significantly less gain than the RL group (M=1.04, SE=0.05; p=0.030; see Figure 5).

Correlations between Assessment Scales and Behavioral Performance

There were no significant correlations between assessment scales and behavioral performance in schizophrenia participants or their relatives. Schizophrenia participants did not show statistically significant correlations between SANS scores and percent error values. Correlation values between percent error during volitional saccade performance and each of the SANS categories including Flat Affect Scale (r=0.34, p=0.30), Alogia Scale (r=0.18, p=0.60), Avolition/Apathy Scale (r=-0.11, p=0.747), Anhedonia/Asociality Scale (r=-0.07, p=0.838), and

Attentional Impairment Scale (r=0.46, p=0.15) were not statistically significant. Schizophrenia participants did not show statistically significant correlations between SAPS scores and percent error values. Correlation values between percent error during volitional saccade performance and each of the SAPS categories including Hallucination Scale (r =0.50), Delusion Scale (r=-0.29, p=0.39), Bizarre Behavior Scale (r=0.13, p=0.703), and Positive Formal Thought Disorder Scale (r-0.36, p=0.28) were not statistically significant. Schizophrenia participants did not show statistically significant correlations between Global Assessment Functioning scores (GAF) and percent error during volitional saccades performance (r=0.23, p=0.50).

Relatives of schizophrenia participants did not show statistically significant correlations between Schizotypal Personality Questionnaire (SPQ) scores and percent error values (r = 0.34, p = 0.25). Additionally, relatives of schizophrenia participants did not show statistically significant correlations between Scores for the Scales of Psychosis Proneness (Chapman & Chapman, 1980) and percent error values. Correlation values between each Scale of Psychosis Proneness and percent error including Magical Ideation Scale (r=0.01, p=0.97), Revised Physical Anhedonia Scale (r = 0.08, p = 0.79), Physical Anhedonia Scale (r=0.25, p=0.41), Revised Social Anhedonia Scale (r=0.43, p=0.14), and Ideation Scale (r=-0.32, p=0.28) were not statistically significant.

FMRI Results

The clustered one-sample *t* map collapsed across groups (NP, RL, SZ) and tasks (AS, ODR) revealed that the following regions showed significant BOLD signal activity during experimental (volitional tasks) compared to baseline (fixation) conditions (see Table 1, see Figure 6): bilateral striatum, bilateral insula, bilateral middle occipital gyrus (MOG), bilateral cuneus, bilateral anterior cingulate gyrus (ACG), bilateral superior parietal lobule (SPL), bilateral lateral frontal

eye fields (lFEF), supplementary eye fields (SEF), bilateral medial frontal eye fields (mFEF), bilateral BA 9 and BA 10 in dorsolateral prefrontal cortex (DLPFC). Thus, these 11 regions in the basal ganglia-thalamocortical circuitry (BGTC) comprised the regions of interest (ROIs) for the current study.

Between-Group Differences. A 3 (group: SZ, RL and NP) X 2 (task: AS and ODR) ANOVA for each defined ROI revealed that there were no effects of task (all p-values from all ROIs were greater than p=0.155). Further neural activity results have been collapsed across tasks because there were no effects of task in behavioral performance or neural activity.

ROI analysis revealed three types of patterns of results when looking for group effects in each BGTC region (see Table 1 and Figure 7). First, all groups showed task-related signal increase in SPL and mFEF (see Figure 8). Although not significant, the relative group tended to show intermediate task-related signal change characterized by weaker task-related signal change than the normal group and stronger task-related signal change than the schizophrenia group in DLPFC (BA 9) and striatum (see Figure 8). Second, the schizophrenia group showed significantly decreased task-related signal change when compared to the normal and relative groups in SEF and lFEF (see Figure 9). Finally, both the schizophrenia and the relative groups showed significantly decreased task-related signal change when compared to the normal group in DLPFC/BA 10, ACG, cuneus, insula and MOG (see Figure 10). Relatives tended to show intermediate task-related signal change in these five regions.

CHAPTER 4

Discussion

The present study is the first fMRI study to examine executive functioning deficits in schizophrenia participants, their first-degree biological relatives, and a normal group by investigating the neural substrates underlying higher-level ocular motor performance. Additionally, the current study optimized behavioral differences between groups by using two different ocular motor tasks to assess different levels of executive functioning components such as inhibition, working memory and volitional saccade generation.

Behavioral results are consistent with previous findings of poor executive functioning in schizophrenia participants and their first-degree relatives. FMRI results revealed differences in patterns of brain activity between groups within the basal ganglia-thalamocortical circuitry: (1) the schizophrenia participants and their relatives showed normal activity in four regions of the circuitry (2) the schizophrenia participants showed decreased task-related signal change in SEF and lFEF when compared to the normal and relative groups, (3) both the schizophrenia participants and their relatives showed decreased task-related signal change in five regions of the circuitry when compared to the normal group. These results suggest that rather than showing a generalized dysfunction in the BGTC circuitry, schizophrenia participants and their relatives show particular disruptions at different levels of the circuitry mediating executive functioning. Additionally, the dysfunction observed in relatives of schizophrenia participants showed to be intermediate between the normal and schizophrenia groups.

Behavioral Differences between Groups

As with previous ocular motor studies, schizophrenia participants and their relatives showed executive functioning deficits revealed by poor performance during AS and ODR tasks (Ettinger et al., 2006; Everling et al., 1996; Fukushima et al., 1990; McDowell et al., 1999, 2001; Radant et al., 2007; Ross et al., 1998, 2000; Sereno & Holzman, 1995). Because statistical analyses showed that AS and ODR performance did not differ and was significantly correlated in all groups, it was assumed that correct performance in both tasks required similar executive functioning components (Hutton et al., 2004). During the rest of the discussion, behavioral performance will be addressed as volitional saccade task performance (AS and ODR task performance combined).

Behavioral Deficits in the Schizophrenia and Relative Groups

Results from this study confirmed abnormalities with both inhibition and working memory in schizophrenia participants and their relatives during volitional saccade performance (Ettinger et al., 2006; Everling et al., 1996; Fukushima et al., 1988, 1990; McDowell et al., 1999, 2001; Park 1997; Radant et al., 2007; Ross et al., 1998, 2000; Sereno & Holzman, 1995). Additionally, results showed that abnormalities found in relatives of schizophrenia participants were intermediate.

Inhibitory problems were evident in schizophrenia participants and their relatives because they failed to inhibit prepotent ocular motor responses by consistently generating an increased number of saccades toward the peripheral cue and/or its location during volitional saccade task performance. In addition to attributing increased number of error saccades to inhibitory deficits (Donohoe et al., 2006; Reuter et al., 2005) previous literature has proposed that increased error rate may be related to working memory problems, in which schizophrenia participants and their

relatives fail to maintain adequate task requirements for correct task performance (Hutton et al., 2004).

Working memory problems in schizophrenia participants and their relatives were evidenced by slower and less accurate volitional saccades. Schizophrenia participants and their relatives generated correct saccadic responses with increased latencies when compared to the normal group, suggesting an impairment in initiating internally driven saccades (Reuter & Kathmann, 2004). Another indication of working memory problems in schizophrenia participants and their relatives was evident in saccadic responses with decreased gain. After the initial saccadic response, the eye movement position of schizophrenia participants and their relatives showed decreased gain in relation to the cued location. It was found however, that after their initial hypometric response, schizophrenia participants and their relatives corrected the accuracy of their eye position because their final eye position was not significantly different from that of the normal group. Similar effects were found in a study by Krappman and Everling (1998), in which they suggest that rather than being a failure in storing the location of the correct cue position, the error of the initial eye position could be a result of a failure to use an internal representation to guide the appropriate behavioral response (Hommer et al., 1991).

As in previous studies, inhibitory and working memory problems in relatives of schizophrenia participants showed to be generally intermediate, showing a pattern of poorer performance than the normal group and better performance than the schizophrenia group (Ettinger et al., 2006; McDowell et al., 1999, 2001; Ross et al., 1998). These intermediate patterns of behavioral performance observed in relatives of schizophrenia participants, suggest that poor performance during volitional saccades tasks requiring executive functioning may be

identified as potential behavioral markers for individuals at risk for schizophrenia (Karoumi et al., 2001; Ross et al., 1998).

Behavioral results from the current study as well as previous literature have shown consistent and reliable inhibitory and working memory deficits in schizophrenia participants. These results suggest that observable executive functioning abnormalities as evaluated by ocular motor tasks are good biological markers of schizophrenia. Confirming evidence for this should be found by examining executive functioning in individuals with genetic predisposition to the disease, such as first-degree relatives of schizophrenia participants. Because relatives of schizophrenia participants did show poor volitional saccade performance in the current study, it can be stated that such behavioral abnormalities are not associated to the presence of the illness, but rather to the genetic predisposition for developing the disease (Gottesman & Gould, 2003). Because the literature on inhibitory and working memory abnormalities in relatives of schizophrenia participants is still inconsistent (Brownstein et al., 2003; Levy et al., 2004) stronger evidence that these executive functioning abnormalities are biological markers of schizophrenia is needed. FMRI data provided this evidence through evaluation of biological mechanisms mediating observable poor executive functioning. FMRI results in the current study identified abnormal neurological markers in both schizophrenia participants and their relatives that are more closely related to the genetic susceptibility for schizophrenia.

Comparison of Neural Circuitry between Groups

Normal participants showed increased BOLD signal change in cortical and subcortical regions of the basal ganglia-thalamocortical circuitry (BGTC) known to support volitional saccadic eye movement (e.g. Camchong et al., 2006, Dyckman et al., 2007; DeSouza et al., 2003; Ford et al., 2005; McDowell et al., 2002; Pierrot Deseilligny et al., 2004; Sweeney et al., 1996,

2007). The BGTC circuitry supporting volitional saccade performance was disrupted in schizophrenia participants and their relatives. The disruptions observed in schizophrenia participants and their first-degree relatives had two important characteristics: (1) the disruption was not generalized across all regions of the BGTC circuitry and (2) the relatives of schizophrenia participants seem to have a lesser degree of disruption. The following sections will review between-group similarities and differences in each of the BGTC circuitry regions of interest, as well as the implications of schizophrenia-related BGTC circuitry dysfunction.

BGTC Regions that Showed no Significant Difference between Groups

The BGTC circuitry disruption observed in schizophrenia participants and their relatives was not generalized across all regions of the circuitry. This suggests that neural abnormalities found in schizophrenia participants and their relatives are not the result of an overall neural disorganization or attenuation, but rather of more specific disruptions.

The present results showed that schizophrenia participants and their relatives had task-related BOLD signal increases comparable to the activation observed in the normal group in particular regions of the BGTC circuitry: BA 9 in dorsolateral prefrontal cortex, medial frontal eye fields (mFEF), superior parietal lobule and striatum (see Figure 8). These cortical and subcortical regions, which have been found to mediate volitional saccade performance in previous studies (Dyckman et al., 2007; Pierrot-Deseilligny et al., 2003b; Sugiura et al., 2004; Sweeney et al., 1996), have reciprocal connections within the BGTC circuitry. BA 9 in DLPFC has direct reciprocal projections to medial frontal eye fields (mFEF), receives input from superior parietal lobule (SPL) in posterior parietal cortex (PPC), and has projections to striatum in basal ganglia (Pierrot-Deseilligny et al., 2004).

BA 9 in Dorsolateral Prefrontal Cortex (DLPFC)

In the present study schizophrenia participants and their relatives showed normal activation in BA 9 in DLPFC when compared to the normal and the relative group. BA 9 activation during volitional saccade task performance has been associated with inhibition, executive control and/or context updating (Dyckman et al., 2007; Sweeney et al., 1996). While some fMRI studies evaluating executive functioning have found comparable task-related BA 9 activation in schizophrenia participants, their biological relatives and normal participants (Raemaekers et al., 2002, 2006a), other studies have found decreased BA 9 activity in schizophrenia participants and their relatives when compared to the normal participants (Camchong et al., 2006; Keedy et al., 2006; Keshavan et al., 2002; MacDonald et al., 2005; McDowell et al., 2002).

Conflicting evidence on schizophrenia-related BA 9 dysfunction during ocular motor tasks is possibly associated with inconsistent methodologies used across studies. For example, some neuroimaging studies select participants by matching behavioral performance across groups (Raemaekers et al., 2002, 2006a) which may eliminate the evaluation of the neural substrates underlying a range of behavioral deficits (Karlgodt et al., 2007). Context effects within stimulus presentation (e.g. position of trial in a block, choice of baseline condition) could be another reason why results from previous studies are not conclusive (Dyckman et al., 2007). Another example of inconsistent methodologies is blocked versus event-related fMRI designs, in which blocked designs are more likely to detect BA 9 differences across groups. These inconsistencies may affect behavioral performance as well as brain activity mediating performance.

It should be noted that even though present results did not find statistically significant differences in task-related signal in BA 9, Figure 8 does show a trend in which schizophrenia participants and their relatives had decreased activity in this region. Because of statistical power

limited by number of participants and scanner strength, results from this study do not necessarily discount the association of poor volitional saccade performance and a disruption in the prefrontal circuitry at the level of BA 9.

Within the BGTC circuitry, DLPFC is connected with cortical and subcortical regions involved in saccadic performance in which all groups showed similar activity. DLPFC has direct reciprocal projections to medial frontal eye fields (mFEF), another BGTC region that all groups showed volitional saccade task-related activity.

Medial Frontal Eye Fields (mFEF)

The present study did not find between group differences in task-related activity in medial frontal eye fields (mFEF). FEF are divided in lateral and medial FEF. Lateral frontal eye fields (LFEF) have been associated with reflexive saccades triggering, while mFEF signal has been associated with volitional saccades triggering and/or inhibition (Gagnon et al., 2002; Simó et al., 2005). Results from a previous multimodal neuroimaging study using EEG and MEG provided further evidence consistent with the role of mFEF in saccadic inhibition (McDowell et al., 2005). McDowell et al. (2005) found that mFEF showed increased preparatory activity before antisaccade than prosaccade generation.

Even though the present study did not find activation differences between groups in mFEF, a previous study in our laboratory did find significantly decreased task-related activity in mFEF of a group of schizophrenia participants when compared to a normal group during ODR task performance (Camchong et al., 2006). Similarly to activity differences in BA 9, the present study also found that task-related signal in mFEF in schizophrenia participants tended to be decreased when compared to the normal and relative groups (see Figure 8). Present results do not

necessarily discount the association of poor executive functioning and a disruption in mFEF in the BGTC circuitry.

Within the BGTC circuitry supporting eye movements, FEF have reciprocal connections with DLPFC and striatum in basal ganglia, send direct projections to superior colliculus, and receive input from parietal eye fields in posterior parietal cortex (PPC; Pierrot Deseilligny et al., 2004; Squire et al., 2003). Literature has shown that mFEF have reciprocal connections with superior parietal lobule (SPL) in PPC in particular, and together they generate signals to initiate a shift of visual attention from fixation (Kelley et al., 2007).

Superior Parietal Lobule (SPL)

The current study did not find significant between-group differences in task-related activity in SPL. Changes in neural activity in superior parietal lobule (SPL) in PPC have been associated with changes in visual attentional modulation, particularly to the periphery (Buchel et al., 1998; Pierrot-Deseilligny et al., 2004). A blocked fMRI study examining the effects of visual attention load found that SPL showed increased signal related to an "attention" condition versus a "no attention" or a "fixation" condition (Buchel et al., 1998). More specifically, an event-related fMRI study examining the neural substrates of attention shifting from fixation and two peripheral locations found that SPL showed increased signal when visual attention, without eye movement, was shifted from fixation to a contralateral peripheral location (Kelley et al., 2007).

The lack of significant between group differences in SPL activity found in the current study suggests that groups did not differ in their ability to shift visual attention to the periphery. Perhaps, poor executive functioning observed in schizophrenia participants and their relatives in this study was not associated with a dysfunction in visual attentional modulations mediated by

SPL. Within the BGTC circuitry, PPC has reciprocal connections with striatum in the basal ganglia (Clower et al., 2005; Squire et al., 2003).

Striatum

The last region in the BGTC circuitry that did not show between group differences in the present study was the striatum. Previous literature suggests that the striatum in basal ganglia can facilitate or inhibit eye movements by sending and receiving output and input from cortical regions in the BGTC circuitry (Condy et al., 2004; Hikosaka & Wurtz, 1983). Because the basal ganglia provide inhibitory connections between the DLPFC and the SC in particular, it is thought to be involved in preventing the triggering of unnecessary saccades (Condy et al., 2004).

Contrary to Raemaekers et al. (2002), the present study did not find significant between-group differences in task-related signal changes in the striatum. Current results are consistent with a previous study that did not find striatum differences between schizophrenia and normal groups (McDowell et al., 2002). There was a tendency, however, for the normal group to show the highest, the relative group to show intermediate, and the schizophrenia group to show the lowest task-related activity.

Present results showed that BGTC circuitry disruptions observed in the schizophrenia and relative groups were not generalized. Schizophrenia participants and their relatives showed normal task-related activity in BA9 of DLPFC, mFEF, SPL and striatum. Since patterns of neural activity in these regions do not resemble patterns of behavioral differences, these regions in the BGTC circuitry may not mediate poor performance found in the schizophrenia and relative groups. Patterns of activity in BA 9 and striatum, although not significantly different between groups, do tend to resemble behavioral difference. Therefore, results from this study do not

necessarily discount the association of poor executive functioning and a disruption in the BA 9 and striatum of schizophrenia participants and their relatives.

BGTC Regions that Showed Significantly Reduced Activity in the Schizophrenia Group

Poor executive functioning found in schizophrenia participants may be associated with disruptions in BGTC regions in which the schizophrenia group showed reduced activity during volitional saccade performance when compared to the normal and relative groups. The schizophrenia group showed significant disruptions in two cortical areas known to mediate volitional saccade performance. Schizophrenia participants showed decreased task-related BOLD signal in lFEF and supplementary eye fields (SEF) when compared to the normal and relative groups (see Figure 9). Increased activity in these two motor regions in frontal cortex has been associated with saccade performance.

Lateral Frontal Eye Fields (lFEF)

The present study found significantly decreased task-related activity in lFEF in the schizophrenia group when compared to the relative and the normal group. Increased activity in lFEF has been associated with saccade triggering (Gaymard et al., 1998). A multimodal neuroimaging study with EEG/MEG (McDowell et al., 2005) showed that lFEF activity reached peak activity during 110–60 msec before antisaccade generation, but later leveled off. McDowell et al. (2005) suggest that early on during a single antisaccade trial, a reflexive saccade toward the cue is programmed as evidenced by increased activity in lFEF, but later stopped. McDowell et al. (2005) hypothesized that after programming a saccade, lFEF receive inhibitory inputs from SEF and/or mFEF.

Significantly reduced lFEF activity in the schizophrenia group observed in the current study implies that BOLD signal in that region did not show a significant change between the baseline

condition (visual fixation) and the experimental condition (AS and ODR). These findings have two possible implications. One possibility is that schizophrenia participants did show lFEF activity during volitional saccade performance, however, the difference in signal change when compared to fixation could have been minimal. This could be the case if fixation is also considered a demanding task (Amador et al., 1995; Paus et al., 1991) so that lFEF in schizophrenia participants also programmed unwanted eye movements during fixation, which also needed to be inhibited. The second possibility is that schizophrenia participants have a connectivity disruption in the BGTC circuitry at the level of lFEF. BGTC circuitry disruptions in the lFEF of the schizophrenia group could be associated with a failure to receive signals from cortical and subcortical regions of the circuitry. BGTC regions such as basal ganglia, posterior parietal cortex, and/or supplementary eye fields (SEF) may fail to send appropriate excitatory signals to lFEF to enhance activity in this region. More research using neuroimaging techniques with better temporal resolution (i.e. event related fMRI, EEG, MEG) as well as connectivity information (diffusion tensor imaging, DTI) will provide information to better understand lFEF disruptions in schizophrenia participants.

LFEF have reciprocal connections with SEF, another BGTC circuitry region in which schizophrenia participants showed significantly decreased activity when compared to the normal and relative groups.

Supplementary Eye Fields (SEF)

Schizophrenia participants failed to generate increased SEF activity during volitional saccade task performance in the present study. Literature suggests that SEF have a role controlling internally generated eye movements during performance of complex learned behaviors (Leigh & Zee, 2006). Even though lesion studies have shown that the SEF are

involved in complex motor programming of several successive saccades (Pierrot-Deseilligny et al., 2003b), a more specific role has been proposed during single saccade tasks (Schlag-Rey et al., 1997; Parton et al., 2007).

As with lFEF, single saccade studies have reported increased activity in SEF before volitional saccades (i.e. antisaccade) than before prosaccades (Schlag-Rey et al., 1997). Schlag-Rey et al. (1997) suggest that the signal to generate correct volitional saccadic responses has to compete with the signal for inappropriate reflexive saccadic responses. Using single-cell recording in SEF of two non-human primates, Schlag-Rey et al. (1997) found that increased SEF activity preceding antisaccade responses offsets the tendency to generate reflexive saccadic responses. A lesion study also confirmed the SEF's role in implementing control when there is a conflict between competing saccadic responses (Parton et al., 2007). Parton et al. (2007) found that a patient with a focal lesion to the left SEF showed impairment when required to select the appropriate saccade response. Parton et al. (2007) suggest that rather than mediating the inhibition of unwanted saccadic responses, SEF increased activity mediates control over situations of ocular motor response conflict.

Although the relative group had poor behavioral performance during volitional saccade tasks, they showed normal activity in these regions. These results suggest that activity in lFEF and SEF may not be associated with increased error rate during volitional saccade performance. Perhaps reduced lFEF and SEF activity observed in schizophrenia participants may be associated with features that accompany the manifestation of the illness such as symptoms, chronicity and/or medication.

BGTC Regions that Showed Significantly Reduced Activity in the Schizophrenia and Relative Groups

Poor executive functioning found in schizophrenia participants and their relatives may be associated with disruptions in BGTC regions in which both the schizophrenia and relative groups showed lower activity during volitional saccade performance when compared to the normal group. The schizophrenia and relative groups showed significant disruption in five cortical regions in the BGTC circuitry previously found to mediate volitional saccade performance (BA 10 in DLPFC, anterior cingulate gyrus, cuneus, middle occipital gyrus and insula; see Figure 10).

BA 10 in Dorsolateral Prefrontal Cortex (DLPFC)

While task-related activity was observed in bilateral BA 10 in normal participants, the relative and schizophrenia groups showed significantly reduced activity in this region. Increased activation in BA 10 in the normal group during volitional saccade performance is consistent with previous fMRI studies (Camchong et al., 2006; Merriam et al., 2001). Decreased activation of prefrontal activity in BA 10 among the relative and schizophrenia group when compared to the normal group is consistent with reports of decreased prefrontal activity during tasks involving maintenance of information (Camchong et al., 2006; Jansma et al., 2004; Perlstein et al., 2001).

As suggested by previous studies, increased activity in BA 10 in the normal group may be associated with the working memory component of tasks requiring executive functioning (Braver et al., 2001; Leung et al., 2004; Sylvester et al., 2003) such as volitional saccade task performance (Camchong et al., 2006; Merriam et al., 2001). Studies supporting the working memory role of BA 10 have proposed that this region may be involved in the maintenance and monitoring of a sub-goal (i.e. “don’t look towards the peripheral cue”) before a correct response is generated (i.e. “look to the opposite location/look towards location after delay”; Sylvester et

al., 2003). A recent study comparing brain activity mediating tasks involving pursuit versus saccades (evaluating velocity versus position of a cue) found that BA 10 may be involved in monitoring spatial locations of cues and position dependent responses (rather than motion dependent responses; Burke & Barnes, 2007).

Anatomical and physiological studies have suggested that the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) are involved in executive control (for reviews see: Duncan, 2001; Miller and Cohen, 2001). Both areas have close reciprocal connections (Bates and Goldman-Rakic, 1993; Paus et al., 2001; Wang et al., 2004), implying that they may be involved in similar cognitive functions. While PFC has been associated with top-down support of task-appropriate behaviors, ACG has been associated with evaluative processes indicating when control needs to be more strongly engaged (Brown & Braver, 2005; MacDonald et al., 2000).

Anterior Cingulate Gyrus (ACG)

Together with decreased activity in BA 10, the relative and schizophrenia groups also showed significantly decreased activity in anterior cingulate gyrus (ACG). Increased ACG activation in normal participants is consistent with previous volitional saccade studies (Brown et al., 2006; Matsuda et al., 2004; Sweeney et al., 1996), particularly when correct responses are generated (Ford et al., 2005). If there is an existing lesion in ACG, volitional saccade performance is compromised (Gaymard et al., 1998; Milea et al., 2003) characterized by increased number of errors and hypometric saccades. Decreased task-related activation in ACG of schizophrenia participants compared to normal participants has been found during tasks requiring executive functioning such as Stroop (Kerns et al., 2005; Weiss et al., 2007; Yucel et al., 2002), visual oddball (Morey et al., 2005) and Go/No-go (Rubia et al., 2001) tasks.

While previous studies have proposed that ACG is involved in error detection and conflict monitoring (Bioulac et al., 2005; Kerns et al., 2004; Miller & Cohen, 2001), recent studies have found that ACG is additionally activated when more executive control is required due to an increase in task demands (Brown & Braver, 2005; Johnston et al., 2007). Evidence for the latter hypothesis was reported in a non-human primate study by Johnston et al. (2007) in which increased ACG activity was observed immediately after an error was generated due to an unexpected task switch. Johnston et al. (2007) propose that activity in ACG increases in order to decrease the probability of generating another consecutive error.

Previous literature together with consistent poor volitional saccade performance in the present study, provide evidence that ACG dysfunction in schizophrenia participants and their relatives may be associated with (1) impairment in error detection and conflict monitoring and/or (2) inability to engage ACG neurons when more executive control is required due to increased task demands.

Cuneus

Another region of the BGTC circuitry in which the normal group showed significant increased task-related signal in comparison to the schizophrenia and relative groups was cuneus in occipital cortex. Increased cuneus activity in the normal population during volitional saccade performance has been previously observed (Camchong et al., 2006; Doricchi et al., 1997; Dyckman et al., 2007; McDowell et al., 2005).

A previous EEG/MEG study reported increased cuneus activity preceding volitional saccade performance and suggested that activity in this region may influence earlier visual association regions like the middle occipital gyrus (McDowell et al., 2005). Poor volitional saccade performance observed in the present study in the schizophrenia and relative group may be

associated with a difficulty in relaying or influencing information to visual areas such as middle occipital gyrus (McDowell et al., 2005; Vanni et al., 2001).

Middle Occipital Gyrus (MOG)

As observed in cuneus, results from the present study showed similar decreased activity in middle occipital gyrus (MOG) in the schizophrenia and relative groups when compared to the normal group. MOG activity has been attributed to different aspects of visual processing. A recent study with normal participants found increased bilateral MOG activation in anticipation of an appearing cue at predictable cued locations (Hahn et al., 2006). This study suggested that increased MOG activation is associated with endogenous or internal allocation of visual attention to predicted cue locations (Hahn et al., 2006).

Studies have also suggested another MOG role emphasizing on the PFC modulation of visual cortex areas including MOG (Miller & Cohen, 2001). Clementz et al. (2007) suggested that MOG receives input from PFC in order to make a decision to move (pro- or anti-saccade trial) or not to move (no-go, fixation trial) the eyes depending on the task's contextual cues. Clementz et al. (2007) found increased MOG and PFC activity during both pro- and anti-saccade trials when compared to no-go (fixation) trials after early (158 msec postcue) stimulus registration. Concurrent increased MOG and PFC activity during volitional saccade performance (AS) suggested that PFC imposed the appropriate decision on MOG whether to move or not move the eyes (Clementz et al., 2007).

It is possible that in the present study the normal group and not the schizophrenia and relative groups showed increased MOG activity as a result of (1) allocating attention to peripheral cue locations (Hahn et al., 2006), and/or (2) receiving a signal from PFC for appropriate eye movement generation or inhibition (Clementz et al., 2007).

Insula

The last region of the BGTC circuitry in which both the schizophrenia participants and their relatives showed lower task-related activity than the normal group was insula. Increased task-related activity in bilateral insula of normal participants during volitional saccade performance has been previously reported (Camchong et al., 2006; Luna et al., 2002; Manoach et al., 2007; Raemaekers et al., 2006b). Decreased task-related activity in this region has been previously observed in schizophrenia participants during volitional saccade task performance in fMRI and PET studies (Camchong et al., 2006; Crawford et al., 1996).

Previous literature has suggested that the insula plays a role in sensory and motor functions. A study evaluating sensory awareness of patients with lesions to either right or left insula found that damage to this region was associated with impaired awareness of external stimuli leading to neglect (Manes et al., 1999). Because increased activity in insula has been observed during volitional saccades versus reflexive saccades, this region may also play a role in spatial attention, working memory, or motivational aspects of ocular motor control (Augustine, 1996).

Decreased insular activity in the present study may mediate poor volitional saccade performance observed in the schizophrenia and relative group. Within the BGTC circuitry, insula has reciprocal connections with SEF, PFC, ACG and PPC (Garavan et al., 1999). Further studies need to be conducted to better examine the role of insula in executive functioning.

In summary, present findings showed that both schizophrenia participants and their relatives had reduced neural activity in five BGTC regions (BA 10, ACG, cuneus, MOG and insula) during executive functioning performance. Because the common factor between these two groups is the genetic predisposition for developing schizophrenia, these findings provide important information for the identification of these particular neural dysfunctions as potential

biological markers for the disease. Additionally, because the relatives of schizophrenia participants do not manifest the illness (e.g. symptoms, chronicity and/or medication), results suggest that these common BGTC circuitry dysfunctions are not due to the illness itself. Therefore, abnormalities in these five regions can be associated with a genetic predisposition to develop schizophrenia which can be identified as biological markers for the disease.

It should also be noted that the pattern of differences in activation in these BGTC regions resembles the pattern of differences in behavioral performance observed across groups (the normal group better than the relative group, and the relative group better than the schizophrenia group). The inclusion of relatives of schizophrenia participants in the current study provided important and novel information about this parametric pattern. Relatives of schizophrenia participants showed an intermediate pattern of neural activity in these five BGTC regions (less activity than the normal group and more activity than the schizophrenia group in BA 10, ACG, cuneus, MOG and insula) as well as an intermediate pattern of behavioral performance (more errors than the normal group, and fewer errors than the schizophrenia group). These results provide evidence that the BGTC regions described above mediate poor volitional saccade performance and may be biological markers of neural dysfunction related to genetic predisposition to the illness.

Potential Limitations and Future Directions

In the present study, functional neuroimaging was an appropriate tool for examining biological markers associated with schizophrenia. In order to complement and strengthen the research investigating biological markers for schizophrenia, however, additional and alternative strategies could be used. First, future studies should evaluate larger samples of participants with a more detailed spectrum of individuals at risk for developing schizophrenia. Evaluating the

individual differences across the schizophrenia spectrum may be helpful to understand genetic polymorphisms that underlie neural dysfunction as well as parametric executive functioning deficits. A larger number of schizophrenia participants will also provide information about effects of antipsychotics on behavior and its mediating neural substrates. Second, the use of neuroimaging techniques that provide better temporal information on the neural events underlying executive functioning will be very useful. Event-related fMRI, EEG and/or MEG are techniques that would allow to (1) distinguish separate elements of task performance, such as preparation for movement or inhibition before a response, (2) identify subtle neural differences that mediate AS and ODR task performance separately, which is precluded with the blocked design, (3) perform separate analysis to examine neural correlates mediating correct versus incorrect trials, and (4) evaluate differences in the latency of neural activity between-groups. Third, the use of neuroimaging techniques (e.g. Diffusion Tensor Imaging) that provide information about structural connectivity between regions in the BGTC circuitry supporting executive functioning will give a better understanding of the nature of the dysfunctions at specific levels of the circuitry. Finally, the addition of genetic analysis of individuals in the schizophrenia spectrum will strengthen the impact of genetic liability for behavioral and neural dysfunction related to the illness.

Conclusions and Summary

The current study provided evidence that schizophrenia participants and their relatives have disruptions in the neural circuitry mediating observable executive functioning deficits. The patterns of neural activity in regions of interest across groups had three important and distinct characteristics. First, disruptions in schizophrenia participants and their relatives were not generalized. Schizophrenia participants and their relatives showed normal neural activity in four

regions mediating volitional saccade performance (BA 9 in dorsolateral prefrontal cortex, medial frontal eye fields, superior parietal lobule and striatum). Second, schizophrenia participants showed disruptions in a number of BGTC regions (lateral frontal eye fields, supplementary eye fields, BA 10 in dorsolateral prefrontal cortex, anterior cingulate gyrus, cuneus, insula, and middle occipital gyrus). Interestingly, the relatives of schizophrenia participants only showed neural dysfunctions in five of these regions (BA 10 in dorsolateral prefrontal cortex, anterior cingulate gyrus, cuneus, insula, and middle occipital gyrus). Additionally, the relatives of schizophrenia participants showed a lesser degree of disruption in these regions. Because relatives of schizophrenia participants have the genetic predisposition for schizophrenia and not the manifestation of the illness, the identification of these neural disruptions allowed us to closer detect neurological markers for vulnerability to the disease. Third, only schizophrenia participants showed disruptions in lateral frontal eye fields and supplementary frontal eye fields. Since relatives of schizophrenia participants showed normal activity in these regions, these regions do not suggest vulnerability to the disease, but may be rather associated with the chronicity of the illness.

By using behavioral measurements together with fMRI techniques, this study provides evidence that abnormal executive functioning and its underlying neural substrates may be heritable in schizophrenia. Results from this study facilitate early identification of behavioral and neural deficits in individuals at risk of developing schizophrenia.

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Table 1
Talaraich coordinates of the centers of mass for each ROI that showed BOLD signal increase associated with volitional task performance in all groups

Anatomy of ROI	L/R	x	y	z
Normal activity in all groups				
DLPFC (BA 9)	L	-45	23	29
	R	38	31	31
MFEF (BA 6)	L	-27	-3	41
	R	26	-1	46
SPL (BA 40)	L	-26	-64	53
	R	24	-64	53
Striatum	L	-15	-2	11
	R	19	-2	11
Reduced activity in Sz group				
LFEF (BA 6)	L	-46	-3	39
	R	44	-5	39
SEF (BA 6)		3	15	40
Reduced activity in Sz and Rl group				
DLPFC (BA 10)	L	-27	54	14
	R	34	53	10
ACG (BA 32 & 24)	L	-10	43	8
	R	15	36	14
Cuneus	L	-11	-76	1
	R	12	-76	1
Insula	L	-39	20	1
	R	42	13	1
MOG (BA 18 & 19)	L	-43	-74	8
	R	28	-82	21

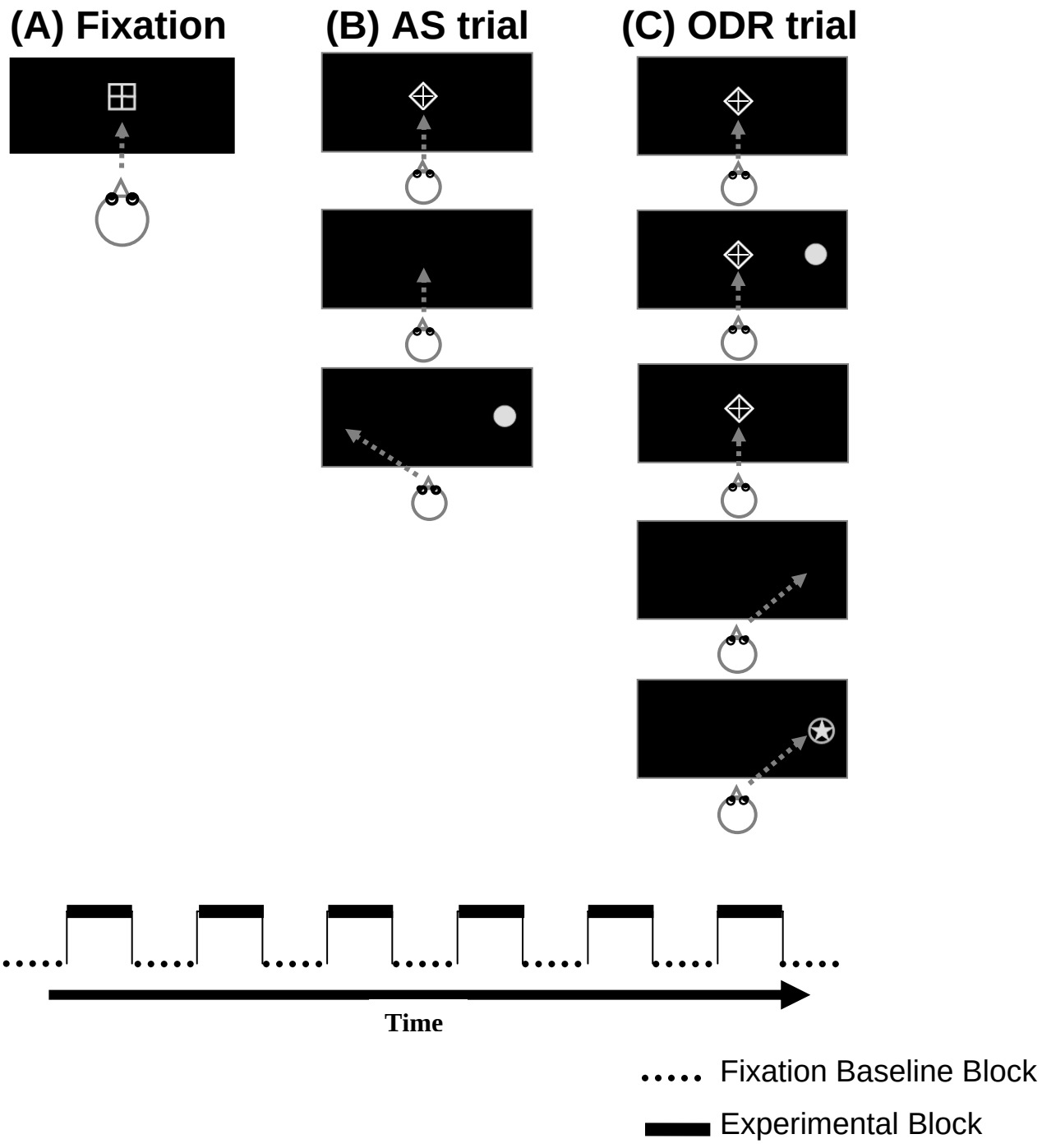


Figure 1. Antisaccade (AS) and Ocular Motor Delayed Response (ODR) Task Trials
Stimuli presented during AS and ODR runs. During the AS run, participants were presented with 22.5-second blocks of fixation (1A) alternated with blocks of eight AS trials (1B). During the ODR run, participants were presented with 22.5-second blocks of fixation (1A) alternated with blocks of six ODR trials (1C). Gray arrows show correct eye position.

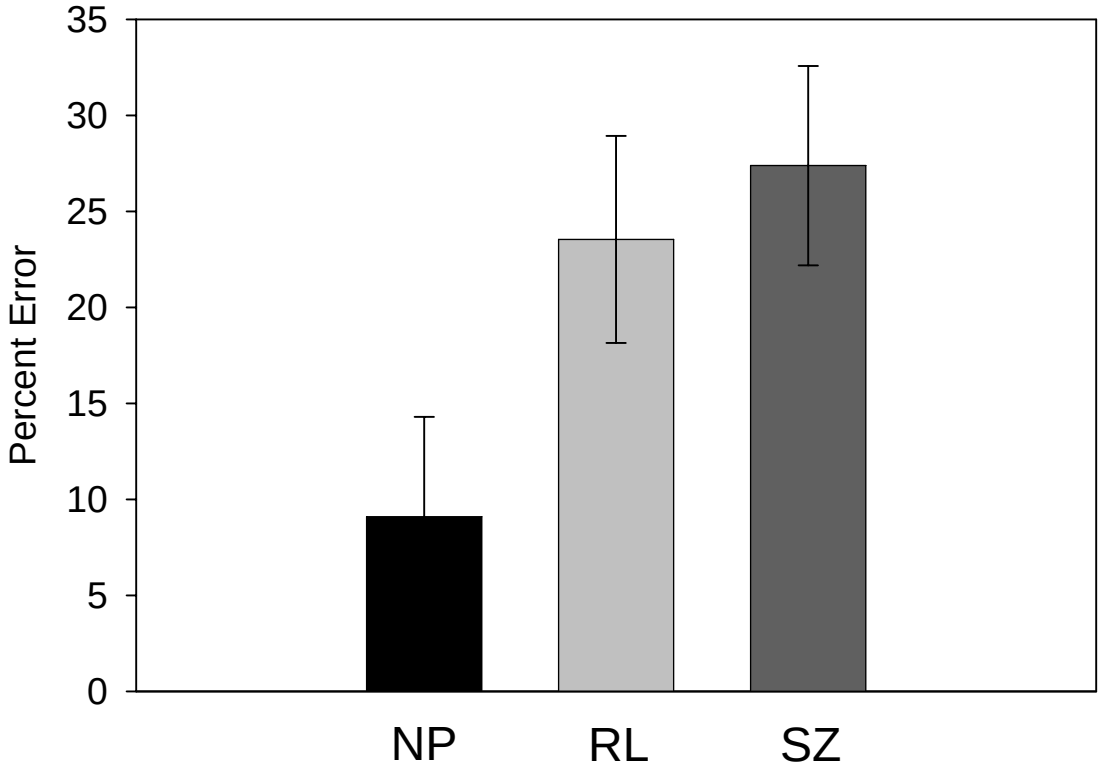


Figure 2. Behavioral Results – Percent Error
Bar graph showing mean percentage of errors (and standard error) generated during volitional saccade performance in the normal group (black), relative group (light gray), and schizophrenia group (dark gray).

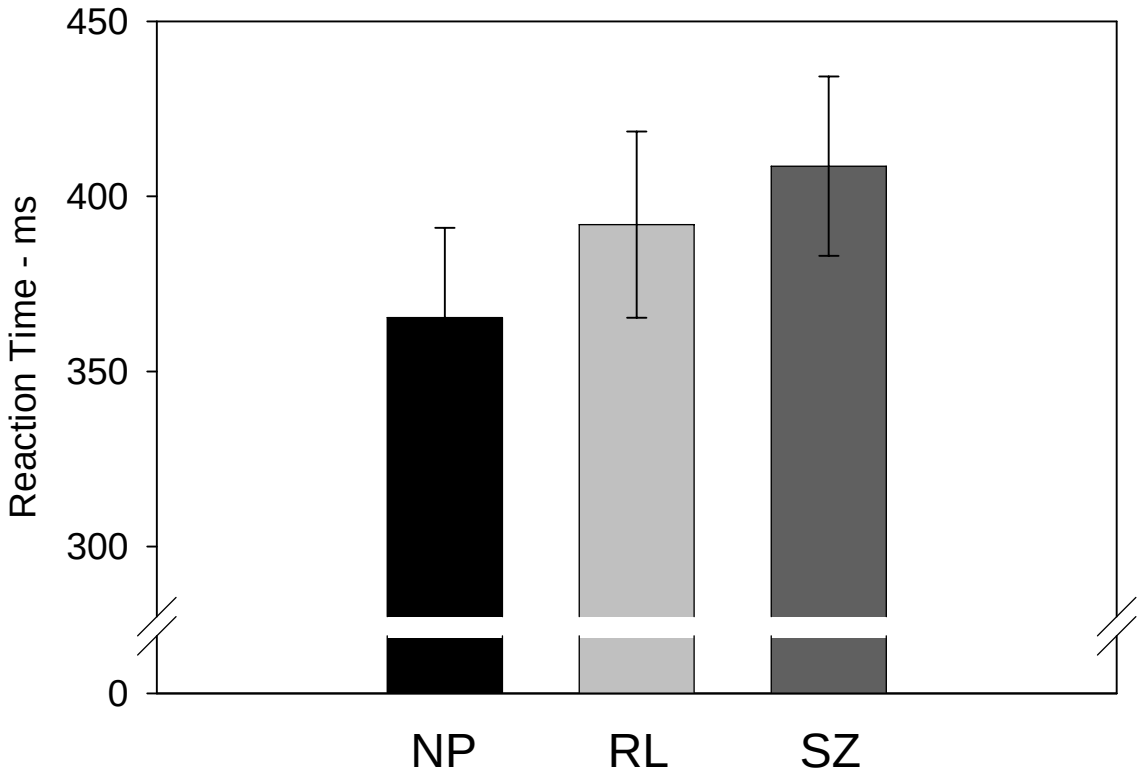


Figure 3. Behavioral Results – Reaction Time
Bar graph showing mean reaction time (and standard error) of responses generated during volitional saccade performance in the normal group (black), relative group (light gray), and schizophrenia group (dark gray).

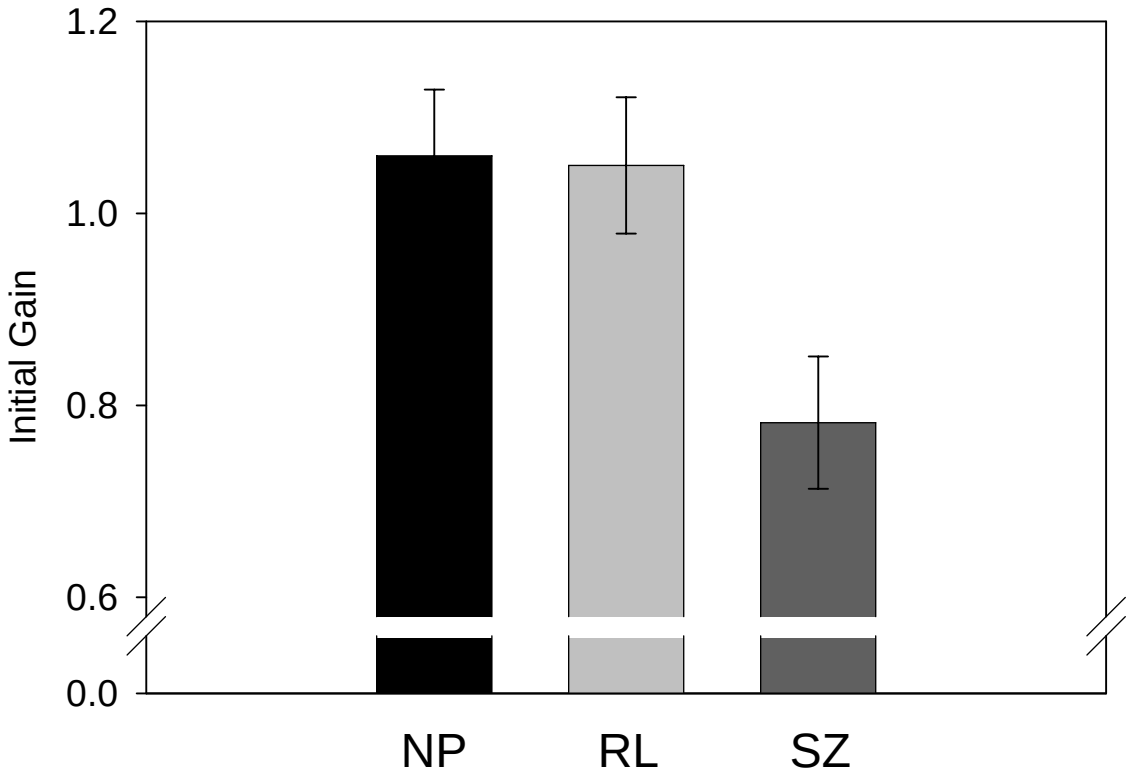


Figure 4. Behavioral Results – Initial Gain
Bar graph showing mean initial gain (and standard error) of correct volitional saccade performance in the normal group (black), relative group (light gray), and schizophrenia group (dark gray).

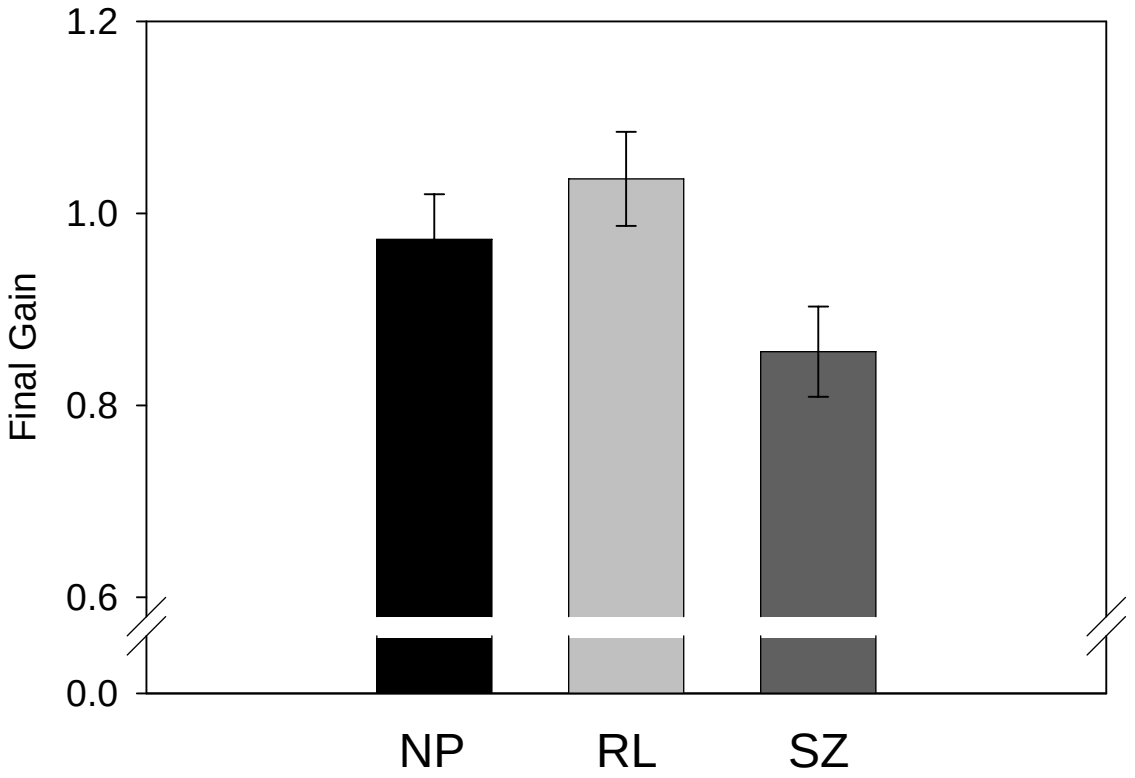


Figure 5. Behavioral Results – Final Gain
Bar graph showing mean final gain (and standard error) of correct volitional saccade performance in the normal group (black), relative group (light gray), and schizophrenia group (dark gray).

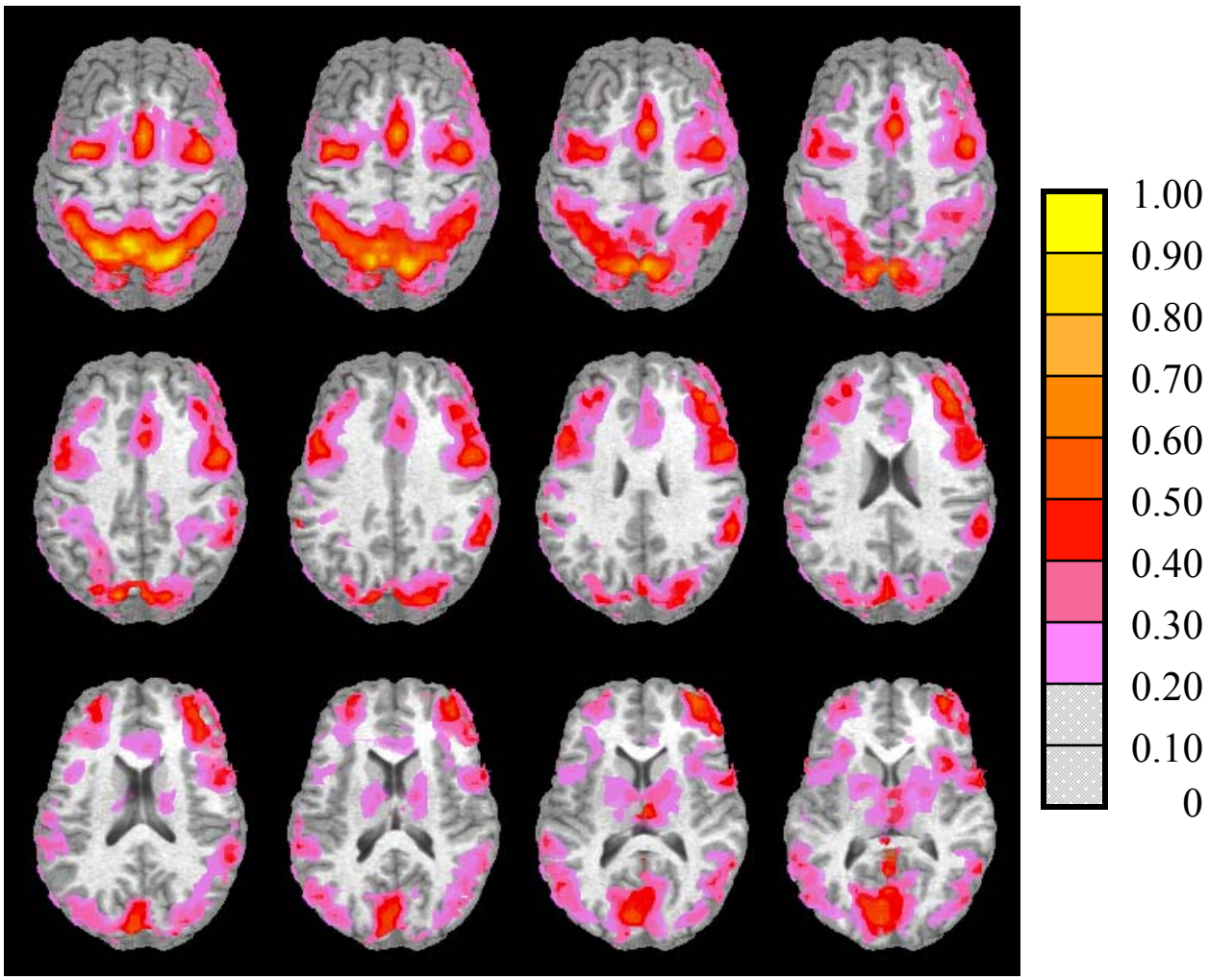
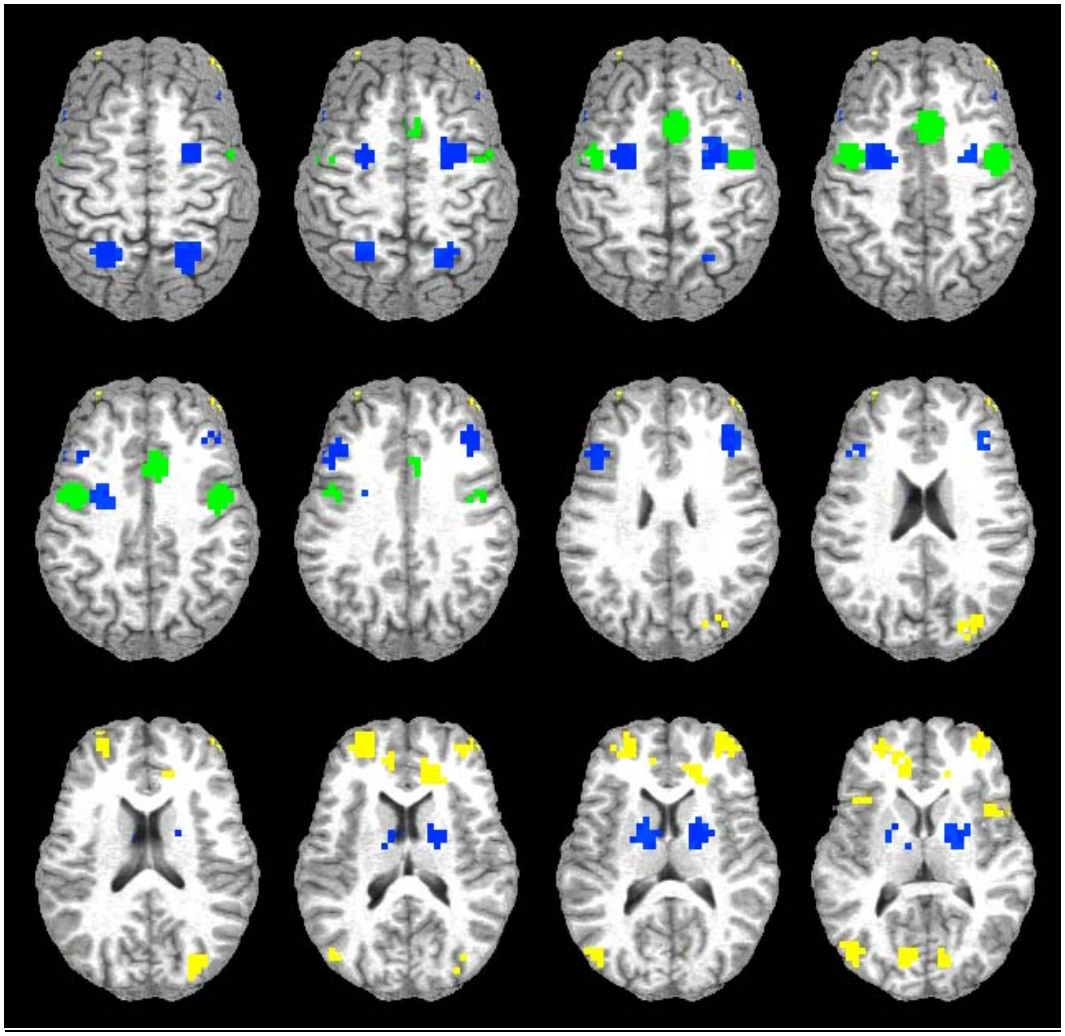


Figure 6. FMRI Results – Whole-Brain Analysis Results for all Groups
Axial slices (top left z = 52 through bottom right z = 12, spacing = 8 mm) displaying regions with significant signal change during AS and ODR performance in all groups. This one-sample t-map was used to determine ROIs. The background anatomical image is a structural image from one subject in neurological convention (left hemisphere on the left).



<u>Figure 7.</u> FMRI Results – Differences between Groups
Axial slices (top left z = 52 through bottom right z = 12, spacing = 8mm) displaying significant BOLD signal changes between volitional task performance (AS and ODR) versus fixation in each group. Areas in which the normal group showed significantly increased task-related signal change compared to the relative and schizophrenia group are shown in yellow. Areas in which both the relative and the normal group showed significantly increased task-related signal change compared to the schizophrenia group are shown in green. Areas in which all three groups showed task-related signal change are shown in blue. The background anatomical image is a structural image from one subject in neurological convention (left hemisphere on the left).

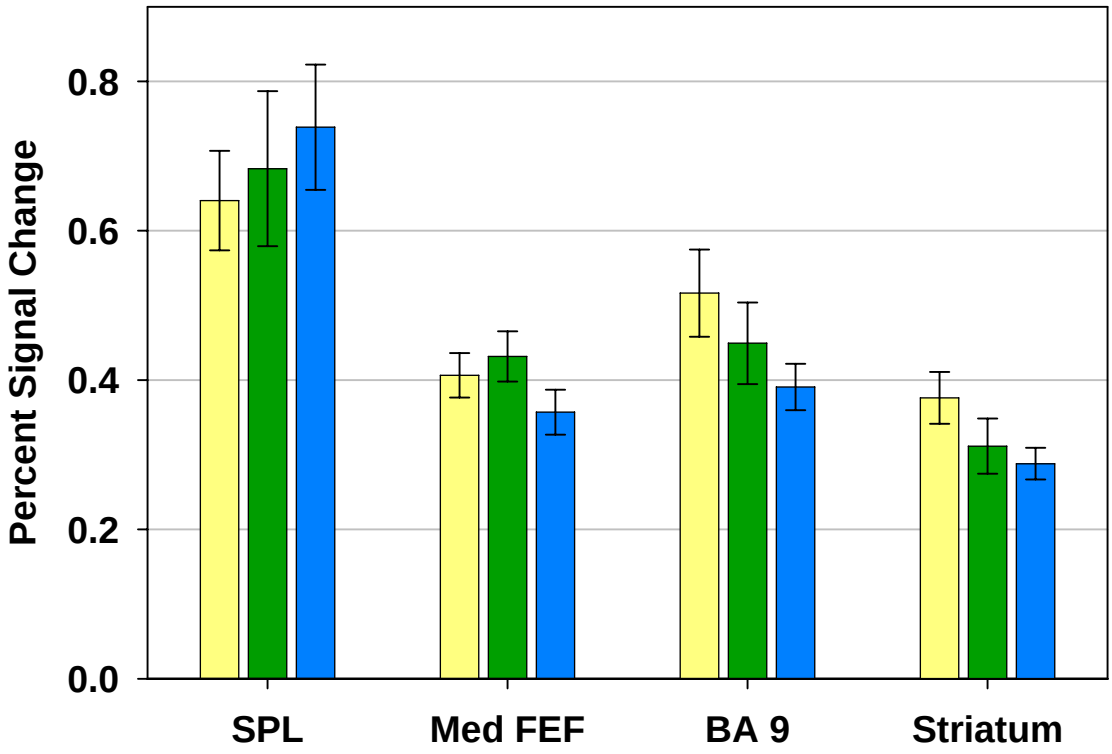
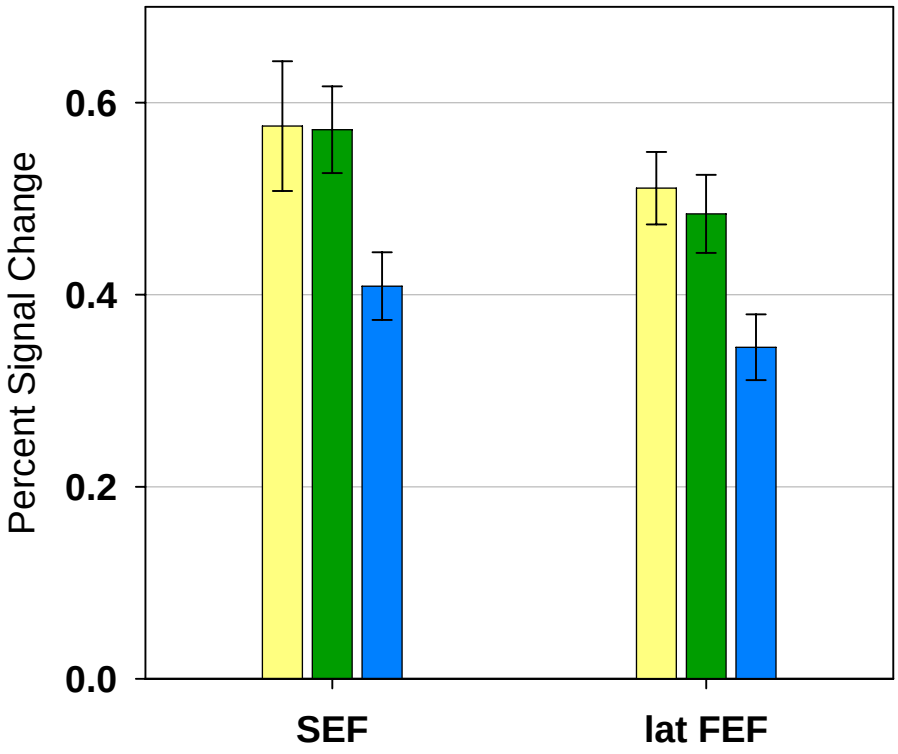


Figure 8. Regions of Interest with no Significant Differences between Groups
Bar graphs showing mean percent signal change (and standard error) for the normal (yellow), relative (green), and schizophrenia (blue) groups. ROIs depicted showed no overall significant differences in task-related signal change between groups.



<u>Figure 9.</u> Regions of Interest in which the Schizophrenia Group Showed Decreased Activation

Bar graphs showing mean percent signal change (and standard error) for the normal (yellow), relative (green), and schizophrenia (blue) groups. ROIs depicted showed overall significant differences between groups. Significantly lower task-related signal change was observed in the schizophrenia group than in the normal and relative groups.

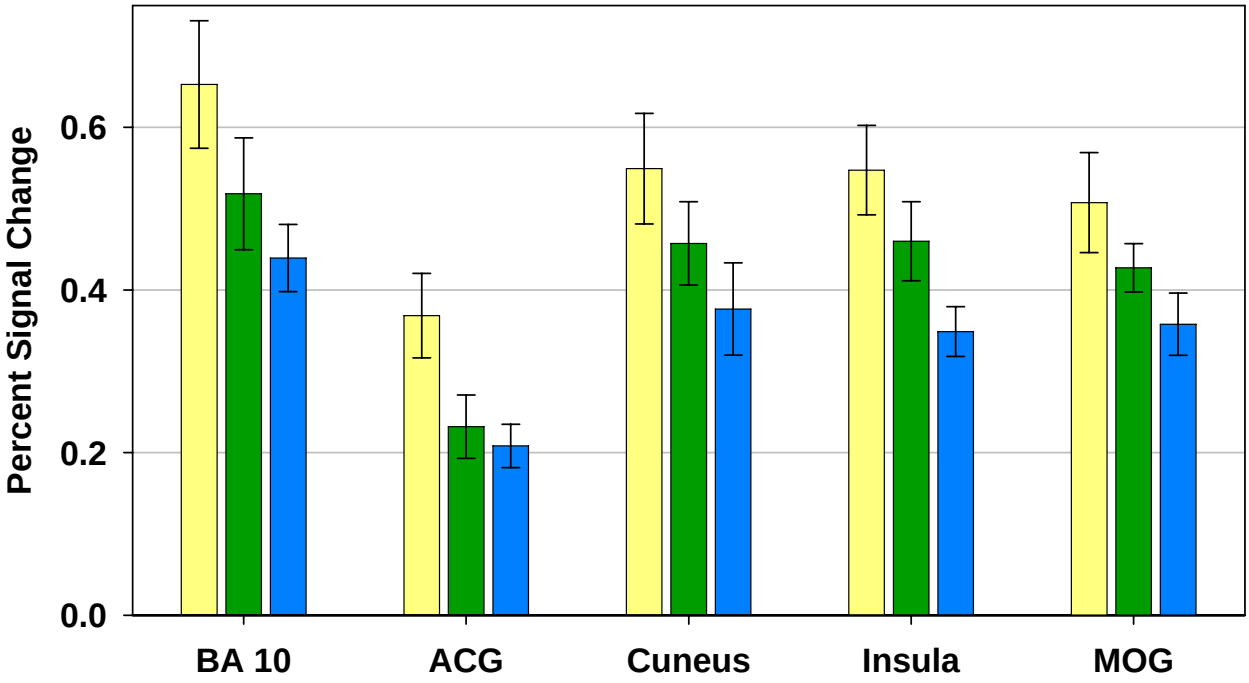


Figure 10. Regions of Interest in which both the Schizophrenia and Relative Groups Showed Decreased Activation

Bar graphs showing mean percent signal change (and standard error) for the normal (yellow), relative (green), and schizophrenia (blue) groups. ROIs depicted showed overall significant differences between groups. Lower task-related signal change was observed in the schizophrenia group than in the normal group. Task-related signal change in the relative group did not differ from either the schizophrenia or normal groups.