PRACTICE-INDUCED CHANGES IN NEURAL CIRCUITRIES SUPPORTING SACCADE PERFORMANCE IN SCHIZOPHRENIA; AN FMRI STUDY

by

BENJAMIN PIYA AUSTIN

(Under the Direction of Jennifer E. McDowell)

ABSTRACT

Decreased prefrontal cortex (PFC) function is hypothesized as a key deficit in people with schizophrenia. PFC circuitry supports higher level executive control processes such as inhibition. A simple test of inhibition is provided by an antisaccade task, which requires a glance to the mirror image of a peripheral cue. People with schizophrenia make more antisaccade errors towards the cue and have lower PFC activity than healthy participants. The extent to which PFC activity may be enhanced to possibly improve executive control in schizophrenia is uncertain. Recent studies from our laboratory showed that in healthy people daily antisaccade practice improves antisaccade performance, while daily prosaccade practice disrupts antisaccade performance. These behavioral changes are accompanied by quantifiable changes in brain activation. The current study was designed to determine whether neural pathways supporting antisaccade performance in schizophrenia are modified across time. People with schizophrenia (SZ) and normal comparison subjects (NP) took part in a 2-week trial. Testing evaluated anti- and pro-saccade performance in a 3-Tesla fMRI environment at 3 time points, each separated by a week; 1) Pre-Test, 2) Mid-Test, and 3) Post-Test. Subjects were assigned to a practice group (either antisaccades or prosaccades) and between fMRI testing sessions completed daily practice sessions on the assigned task. In order to determine if improved executive functioning processes

could be generalized beyond the practice task, other measures of executive function were evaluated before and after the practice trial using both saccade (ocular motor delayed response task – ODRT) and non-saccade tasks (the Wisconsin Card Sorting Test - WCST). The behavioral results showed that both the SZ and NP prosaccade practice groups demonstrated similar behavioral performance patterns across time (decreased latencies and sustained performance) while the SZ and NP antisaccade practice groups demonstrated incongruent patterns (the SZ group showed a trend for improved antisaccade performance with speed-accuracy tradeoffs while the NP group did not). The imaging results across groups illustrated typical saccadic circuitry in regions known to support antisaccade performance, and all groups demonstrated a trend for decreased PFC across time. Within the schizophrenia group, however, there was a small subset of participants who showed increased PFC activity from pre-test to post-test, and this reversal of hypofrontality was correlated with improved performance on various WCST measurements including, most notably, a decrease in rate of perseverative errors.

INDEX WORDS: Schizophrenia, Plasticity, fMRI, Saccades, Practice, Prefrontal Cortex

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BENJAMIN PIYA AUSTIN

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BENJAMIN PIYA AUSTIN

Major Professor:	Jennifer E. McDowell
Committee:	Brett A. Clementz Nash Unsworth

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
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DEDICATION

This dissertation is dedicated to my family – Mom, Dad, and Randall - without whom none of this would be possible.

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CHAPTER 1

INTRODUCTION

Decreased prefrontal cortex (PFC) function, or hypofrontality, is hypothesized as a key deficit in people with schizophrenia (Davidson & Heinrichs, 2003; Glahn, et al., 2005; Hill, et al., 2004; Weinberger, Aloia, Goldberg, & Berman, 1994). PFC circuitry supports higher level executive control processes such as planning, working-memory, and inhibition, deficits of which are hallmark characteristics of schizophrenia. Dysfunction of PFC circuitry in schizophrenia can be successfully modeled with executive function tasks including cognitively complex saccadic eye movement tasks. Saccades are fast redirections of gaze that share common neural circuitry from the basic prosaccades (glances towards a peripheral stimulus) to the more complex antisaccades (glances towards the mirror image of a peripheral stimulus) which recruit additional, primarily frontal, regions to support task performance. Schizophrenia and normal participants perform similarly on prosaccade tasks (e.g. latency, accuracy; (Clementz, McDowell, & Zisook, 1994; Fukushima, Fukushima, Morita, & Yamashita, 1990; McDowell & Clementz, 1997)) but schizophrenia participants make more errors on antisaccade tasks (Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; Katsanis, Kortenkamp, Iacono, & Grove, 1997; G. K. Thaker, et al., 2000) which presumably reflects inadequate activation of prefrontal cortex circuitry (Pierrot-Deseilligny, 1994).

Saccadic performance and the neural substrates underlying task performance, such as PFC, can be modified over time with practice in healthy participants, but this has

not yet been studied in people with schizophrenia. Previous studies from our laboratory show that task-consistent practice improves performance (antisaccade practice improves antisaccade performance) while task-inconsistent practice (prosaccade practice) worsens antisaccade performance in healthy people (Dyckman & McDowell, 2005). These behavioral changes have also been associated with corresponding alterations in brain activity patterns which may result from modulations of existing circuitry or a cortical reorganization in which new circuitry is built as a behavior becomes more automatic (Kelly & Garavan, 2005). After one week of daily practice of saccade tasks (prosaccades or antisaccades), healthy participants demonstrate decreased activation of right PFC during antisaccades even though many saccade-related regions showed stable activation over time (Dyckman et al., manuscript in preparation). To our knowledge, however, manipulation of saccadic performance by way of practice has not been reported among people with schizophrenia.

The goal of the current study is to investigate neural plasticity associated with daily practice of saccadic tasks among schizophrenia and normal participants. The manner in which schizophrenia participants' brains respond to consistent and inconsistent practice may have important implications for understanding the malleability and durability of neural mechanisms supporting executive functioning processes within this group. In order to determine if improved executive function can be generalized beyond the practice task, other measures of executive control will be evaluated before and after the practice trial using both saccade (ocular motor delayed response task (ODRT)) and non-saccade tasks (the Wisconsin Card Sorting Test (WCST).

Below is a literature review which begins with background information and builds towards specific aims for the study. As there are no previous studies on schizophrenia and eye movement practice, hypotheses are largely based on information drawn from eye movement research in schizophrenia and practice studies in healthy participants. Background information will be presented in the following order: *Saccades*; *Schizophrenia and Saccades*; *Saccades and Practice (Behavioral Changes* and *Neural Plasticity)*. The review is completed with the *Current Study* and *Specific Aims.*

CHAPTER 2

LITERATURE REVIEW

Saccades

Saccade tasks are an effective means for investigating models of cognitive control for several reasons: 1) the system is particularly well understood based on extensive literature that ranges from single-unit recordings in primates (Johnston & Everling, 2008) to lesion studies in humans (C. Pierrot-Deseilligny, Milea, & Muri, 2004), 2) there is good convergence between that literature and the human functional neuroimaging studies, and 3) saccades can be measured precisely and with a number of reliable parameters (Smyrnis, 2008). As such, the study of cognitive control via saccadic system manipulations has applications across a diverse range of topics, extending from studies of basic motor function to normal cognitive neuroscience studies of executive control to investigations of behavioral and brain activity correlates of psychiatric conditions (McDowell, Dyckman, Austin, & Clementz, 2008a).

The hierarchy of saccades offers the ability to study different cognitive processes and can be organized from more 'automatic' to more 'purposeful' responses (Leigh & Zee, 1999). For example, prosaccades are simple, exogenously-driven redirections of gaze while antisaccades are more complex, endogenously-driven redirections of gaze which, in addition to the cognitive demands required by prosaccades (visuo-spatial attention and generation of a saccade), require inhibitory control, working memory, and

generation of a saccade to a specific spatial location in the absence of a visual target. Correct antisaccade performance requires participants to maintain the instruction to generate a saccade to the peripheral cue's mirror image location, to inhibit a reflexive saccade toward that cue upon presentation, and then to program and generate a saccade to the cue's mirror image location. An error is defined as an initial glance toward the peripheral cue.

Neural regions that comprise saccade circuitry have been identified through animal (Bruce, Goldberg, Bushnell, & Stanton, 1985; Funahashi, Chafee, & Goldman-Rakic, 1993; Schlag-Rey, Amador, Sanchez, & Schlag, 1997), lesion (C. Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, et al., 2003), and neuroimaging studies (McDowell, et al., 2002; O'Driscoll, et al., 1995; Paus, 1996; Raemaekers, et al., 2002; Sweeney, et al., 1996). The network involved in simple prosaccade generation includes subcortical (striatum, thalamus, and superior colliculus (SC)) and other cortical structures (frontal eye fields (FEF), supplementary eye field (SEF), posterior parietal cortex (PPC), and primary visual and extrastriate cortex) (McDowell, Dyckman, Austin, & Clementz, 2008b). Saccades are generated finally by the SC, which receives inputs from 1) the basal ganglia which modify reactivity of the SC through tonic inhibition (Hikosaka, Takikawa, & Kawagoe, 2000) and 2) cortical regions (FEF, SEF, PPC) which are integrated in the ventral layers of the SC.

In addition the basic prosaccade circuitry, performance of volitional saccades (such as antisaccades) requires recruitment of additional neural regions to support the requisite higher-level cognitive processes (Munoz & Everling, 2004; Ch Pierrot-Deseilligny, Muri, Nyffeler, & Milea, 2005; Sweeney, Luna, Keedy, McDowell, &

Clementz, 2007). For antisaccades, PFC is hypothesized to mediate inhibition associated with correct performance (C. Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Sweeney, et al., 1996). Numerous fMRI studies have shown PFC activation during antisaccades but not during prosaccades (e.g. DeSouza, Menon, & Everling, 2003; Matsuda, et al., 2004; McDowell, et al., 2002; Muri, et al., 1998), and this inhibition-related activity appears to precede response generation and is specific to correct anti-trials (DeSouza, et al., 2003; Ford, Goltz, Brown, & Everling, 2005; Matthews, Flohr, & Everling, 2002; McDowell, et al., 2005).

The PFC activity associated with antisaccades may be specific to a region called the dorsolateral prefrontal cortex (DLPFC). This brain region includes the superior and middle frontal gyri (BA 9 & 46; (Petrides & Pandya, 1994)) and clearly supports higher cognitive functions, such as attention, planning, spatial orientation, and behavioral restraint (Goldman-Rakic, 1995; Miller & Cohen, 2001). Lesions studies report that damage to DLPFC does not result in changes to prosaccade performance; however, patients with discrete lesions of the region make more antisaccade errors (C. Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, et al., 2003; C. Pierrot-Deseilligny, Muri, Ploner, Gaymard, & Rivaud-Pechoux, 2003; C. Pierrot-Deseilligny, et al., 1991). Neuroimaging studies (fMRI (DeSouza, et al., 2003; Ford, et al., 2005) and EEG (McDowell, et al., 2005)) suggest that DLPFC is activated prior to antisaccade generation, which is consistent with the putative role of DLPFC in the inhibition of an unwanted saccade toward the peripheral cue.

PFC activity is also demonstrated during other tasks that require inhibition (e.g. Garavan, Ross, & Stein, 1999; Kelly, et al., 2004; Konishi, et al., 1999; Rubia, Smith,

Brammer, & Taylor, 2003), such as ODRT which requires both inhibitory and spatial working memory processes (e.g., Funahashi, Bruce, & Goldman-Rakic, 1989; Funahashi, et al., 1993; Inoue, Mikami, Ando, & Tsukada, 2004; Sweeney, et al., 1996). In ODRT, participants are instructed to remember the location of a peripherally presented visual target through a delay period (spatial working memory component) without making anticipatory saccades (inhibition component), and then to generate a saccade to that (unmarked) location after the delay period. Evidence from the human brain imaging literature demonstrates increased ODRT-related activity in basic saccade circuitry but with special emphasis on parietal and frontal regions (e.g., Berman & Colby, 2002; Brown, et al., 2004; Camchong, Dyckman, Chapman, Yanasak, & McDowell, 2006; Chafee & Goldman-Rakic, 2000; Curtis & D'Esposito, 2006; Geier, Garver, & Luna, 2007; Inoue, et al., 2004; Keedy, Ebens, Keshavan, & Sweeney, 2006; Luna & Sweeney, 1999; Ozyurt, Rutschmann, & Greenlee, 2006; Postle, Berger, Taich, & D'Esposito, 2000; Schluppeck, Curtis, Glimcher, & Heeger, 2006; Srimal & Curtis, 2008; Sweeney, et al., 1996), with considerable neurophysiology evidence suggesting that DLPFC, specifically, supports ODRT performance (Chafee & Goldman-Rakic, 1998, 2000; Funahashi, et al., 1989; Funahashi, et al., 1993; Kojima & Goldman-Rakic, 1982; Takeda & Funahashi, 2002; Tsujimoto & Sawaguchi, 2004). DLPFC may be performing multiple functions during ODRT, including inhibition (e.g., Camchong, et al., 2006; Ford, et al., 2005; McDowell, et al., 2002; Perlstein, et al., 2003) and maintenance of spatial information over time to support memory-guided saccade performance (D'Esposito, Ballard, Zarahn, & Aguirre, 2000; Geier, et al., 2007; Ploner, Gaymard, Rivaud, Agid, & Pierrot-Deseilligny, 1998; Ploner, et al., 2000; Postle, et al., 2000).

Schizophrenia & Saccades

People with schizophrenia perform normally on basic saccade tasks (prosaccades) but demonstrate disrupted performance on saccade tasks that require executive control processes, such as inhibition and working memory (e.g., antisaccades). Previous studies report that schizophrenia and normal participants perform similarly on prosaccade tasks in measurements of latency and spatial accuracy (Clementz, et al., 1994; Crawford, Haeger, Kennard, Reveley, & Henderson, 1995; Ettinger, et al., 2006; Fukushima, et al., 1990; Hutton & Kennard, 1998; Iacono, Tuason, & Johnson, 1981; McDowell & Clementz, 1997; Smyrnis, et al., 2004; G. Thaker, et al., 1989), suggesting that the neural circuitry supporting basic saccade performance may be intact in schizophrenia.

For more cognitively complex saccade tasks such as the antisaccade task, however, schizophrenia participants perform worse than healthy participants (Fukushima, et al., 1994; Katsanis, et al., 1997; G. K. Thaker, et al., 2000). People with schizophrenia generate more errors (glances *toward*, rather than away from, the cue) during antisaccade tasks (Calkins, Iacono, & Curtis, 2003; Curtis, Calkins, Grove, Feil, & Iacono, 2001; Ettinger, et al., 2004; Ettinger, et al., 2006; Karoumi, et al., 2001; Katsanis, et al., 1997; McDowell, Myles-Worsley, Coon, Byerley, & Clementz, 1999; Radant, et al., 2007; Ross, et al., 1998) and demonstrate increased latencies and decreased spatial accuracy of correct responses (Ettinger, et al., 2004; Ettinger, et al., 2006). Inhibitory errors are generated despite participants being engaged in the task and understanding the task demands, which is demonstrated by self-correction of inhibitory errors at a rate similar to their healthy counterparts (Gooding & Tallent, 2001; McDowell, et al., 1999) and

sensitivity to changes in task parameters (i.e. appropriate changes in latency associated with changes in attentional manipulation) (McDowell & Clementz, 1997).

People with schizophrenia also show disrupted performance on other saccade tasks that require inhibition and working memory, such as ODRT. Many studies report that schizophrenia participants generate correct memory saccades that are typically slower and less accurate than memory saccades in healthy participants (Everling, Krappmann, Preuss, Brand, & Flohr, 1996; McDowell, et al., 2001; McDowell & Clementz, 1996; Park, Holzman, & Goldman-Rakic, 1995; Reilly, Harris, Khine, Keshavan, & Sweeney, 2007; Ross, et al., 1998), but the measure that best differentiates groups is an increased frequency of inhibitory errors (anticipatory saccades during cue presentation or during the delay period) in schizophrenia participants (Broerse, Holthausen, van den Bosch, & den Boer, 2001; McDowell, et al., 2001; McDowell & Clementz, 1996). The similar patterns in deficits between antisaccades and ODRT may be due to their similarities in task demand as both require visual spatial attention, inhibition, spatial working memory, and generation of a volitional saccade to an unmarked location.

People with schizophrenia also show differences from healthy people in the neural activation patterns supporting saccadic performance. During volitional saccade tasks, both medicated (Camchong, et al., 2006) and unmedicated (Keedy, et al., 2006) schizophrenia participants show reduced activation in basic saccade circuitry as well as in PFC. In the antisaccade task specifically, people with schizophrenia demonstrate decreased activation in striatal (Raemaekers, Ramsey, Vink, van den Heuvel, & Kahn, 2006) and prefrontal regions (Ford, et al., 2005; McDowell, et al., 2002).

Disrupted performance of complex saccade tasks such as antisaccades and ODRT is characteristic not only of schizophrenia participants but also of their biological relatives. First-degree biological relatives of schizophrenia participants show saccadic abnormalities similar to patients (Crawford, et al., 1998; McDowell, et al., 1999; G. K. Thaker, et al., 2000), suggesting that disrupted performance in patients is not due to medication or sequelae of a chronic illness. Instead, errors in inhibiting the initial glance to the cue (such as in the antisaccade or ODR tasks) could reflect inadequate activation of prefrontal cortex circuitry (Pierrot-Deseilligny, 1994).

Similar patterns of abnormalities of brain activation are also observed in first-degree biological relatives of schizophrenia participants during complex saccade tasks (antisaccade (Raemaekers, et al., 2006); ODRT (Keshavan, et al., 2002)). In a previous fMRI study from our laboratory, both schizophrenia participants and their first-degree biological relatives demonstrated decreased BOLD activity associated with antisaccades and ODRT when compared with healthy participants. The regions that demonstrated deficits included middle occipital gyrus, insula, cuneus, anterior cingulate, and Brodmann area 10 in prefrontal cortex. There were, however, additional regions of decreased activity observed only in the schizophrenia group in lateral FEF and SEF, suggesting a change associated specifically with disease manifestation.

Saccades & Practice

Behavioral Changes

It is currently unclear whether inhibitory processes can be bolstered to improve antisaccade performance in schizophrenia though there is such evidence for healthy participants. Previous studies in the literature suggest that saccadic performance is

indeed malleable in healthy participants; after task-consistent practice (i.e. practice and testing on the same task), prosaccade latencies are decreased (Fischer & Ramsperger, 1986) and fewer antisaccade errors are generated (Dyckman & McDowell, 2005; Fischer, Hartnegg, & Mokler, 2000). Thus, in schizophrenia participants, daily antisaccade practice may also lead to improved performance, but no such study has yet been performed. Instead, evidence on the topic must be drawn from test-retest studies (excluding those studies that manipulate medication status as a variable, e.g., (Harris, Reilly, Keshavan, & Sweeney, 2005; Muller, Riedel, Eggert, & Straube, 1999; Reilly, Harris, Marvin, Keshavan, & Sweeney, 2005; Sweeney, et al., 1997)) that provide multiple exposures to the antisaccade task.

In studies that have small sample sizes, few trials, and/or low error rates the test-retest stability of antisaccade error rate in healthy participants has been reported as moderate (Klein & Berg, 2001; Roy-Byrne, Radant, Wingerson, & Cowley, 1995). Without range of restriction, however, antisaccade error test-retest reliabilities improved (internal consistency (Cronbach's alpha)=0.79; (Ettinger, et al., 2003)), especially for large samples (n=117, test-retest correlation = 0.68; (Klein, Foerster, Hartnegg, & Fischer, 2005)). Finally, a recent study from our laboratory of undergraduates (n=32) demonstrated an antisaccade test-retest error rate correlation of 0.60 (McDowell et al., manuscript in preparation) which further corroborates the stability of antisaccade error rates in healthy participants.

Antisaccade performance in schizophrenia is characterized by higher variability of error rate than their healthy counterparts (McDowell, et al., 1999), but stability of performance across time is similarly stable. Previous studies show that antisaccade

performance across two time points is highly correlated in both schizophrenia participants (r=0.87; (Gooding, Mohapatra, & Shea, 2004)) and in a group of schizophrenia participants and their relatives (r=0.72; (Calkins, et al., 2003)). Recent studies from our laboratory (unpublished) also provide evidence for high stability of performance over time (r=0.94) for a group of healthy, schizophrenia, and first-degree relatives of schizophrenia participants (N=10) who were tested on the antisaccade task twice with an intervening 4-year period.

Although evidence suggests that antisaccade error rates are at least moderately to highly stable in schizophrenia participants, the question remains as to whether saccadic performance variables can be changed as a result of actual practice. Previous studies report improved performance after training on other executive functioning tasks, such as the WCST (Rossell & David, 1997) which, like the antisaccade task, is hypothesized to be mediated by prefrontal cortex circuitry (Baddeley, 1986; Goldman-Rakic & Selemon, 1997). Thus, as schizophrenia participants practice antisaccades, they are similarly expected to improve performance. The proposed study is the first known to investigate this question using saccade performance in schizophrenia.

Neural Plasticity

In addition to the behavioral changes observed with task-consistent practice, neural circuits supporting task performance can also be altered over time with repeated exposure, a concept know as *neural plasticity*. There are three main patterns of activation changes that have been observed after practice (see Kelly & Garavan, 2005 for a review): 1) Decreased activation in the same anatomical structures supporting the initial performance skill, suggesting increased efficiency of the neural circuitry, 2) Increased

activation in the same anatomical structures supporting the initial performance skill, suggesting strengthened activity in task-related areas or an expansion of the cortical representation, and 3) Activation in new cortical regions suggesting functional reorganization.

When healthy subject practice saccade tasks, modulation (decreased or increased activation) of the neural circuitry supporting task performance is observed. After one week of daily practice of saccade tasks (prosaccades or antisaccades), healthy people demonstrate decreased activation associated with antisaccades in right PFC and increased activation associated with both anti- and pro-saccades in posterior cingulate cortex (Dyckman et al., manuscript in preparation). The decreased activation observed during the antisaccade task is often seen with the practice of higher cognitive tasks (see Chein & Schneider, 2005 for a review) and is supported by a previous fMRI study which suggests that as motor movements become more automatic, the motor regions supporting the movement show decreased activation as a result of improved efficiency (Wu, Kansaku, & Hallett, 2004). Decreased activation is observed in both ocular motor (Dyckman study) and motor (Wu study) regions as both systems are supported by parallel substrates (Leigh & Zee, 1999).

Thus, as normal participants practice antisaccades and improve performance by generating fewer errors and faster saccades, PFC activity is expected to decrease as the task become more automatic (e.g. Jansma, Ramsey, Slagter, & Kahn, 2001; Tomasi, Ernst, Caparelli, & Chang, 2004). For schizophrenia participants, however, a group with suspected hypofrontality (Weinberger, et al., 1994), it is hypothesized that practice-associated improvement may be mediated by *increased* PFC activity. This has been

demonstrated previously in a fMRI study by Wexler et al. (2000) – as schizophrenia participants improved on a verbal working memory task they showed increased activation in left inferior frontal cortex with training. Thus, we hypothesize that as a result of task-consistent training, schizophrenia and normal participants will show a dissociation of brain activity patterns during antisaccade testing.

Finally, should increased region specific activity be observed among schizophrenia participants, it raises the question of whether reversal of hypofrontality associated with antisaccade practice has other advantages. Given the putative role of PFC in executive functions (Lezac, 1995) and relationships between antisaccade performance and other measures of executive control (e.g., ODRT and WCST), increased PFC activity may be associated with improved performance on these tasks as well. The ODRT can be used as a direct measure of changes due to practice on a related, but distinctly different saccade task, and the WCST can be used as a means of evaluating whether changes in executive control can be generalized beyond saccade tasks. Importantly, if a relationship exists between better PFC functioning and other executive functioning skills, then practice-induced changes in antisaccade performance could predict which participants are more likely to respond positively during functional rehabilitation.

Current Study

Participants in this study took part in a two-week trial. Pro- and anti-saccade performance were tested in the fMRI environment at three time points (Pre-, Mid-, and Post-Test). Between tests, participants visited the eye movement laboratory daily to practice either pro- *or* anti-saccade tasks. FMRI BOLD data were analyzed across time.

Eye movement data were evaluated for all fMRI and behavioral testing sessions. Pre- and Post-Test measures of executive functioning were assessed by ODR and WCST. These data provide numerous comparisons, but those of greatest interest are grouped below into two specific aims.

Specific Aims

Specific Aim 1

Among schizophrenia participants, behavioral performance following practice will show patterns similar to that documented in normal participants.

Hypothesis 1a: Schizophrenia participants who practice prosaccades will show decreased prosaccade latencies across time.

Hypothesis 1b: Schizophrenia participants who practice antisaccades will show decreased antisaccade errors across time. Measures of antisaccade performance demonstrate that schizophrenia participants make more errors than normal participants. While both groups will benefit from practice, the hypothesized hypofrontality associated with the schizophrenia group may cause behavioral changes to be slower and less extensive than that in the normal group.

Hypothesis 1c: Schizophrenia participants who practice prosaccades will show increased antisaccade errors. By increasing the salience of the cue through prosaccade practice, normal participants make more antisaccade errors. It is expected that this effect will be exaggerated for the schizophrenia participants.

Specific Aim 2

Among antisaccade-practiced schizophrenia participants, there will be a divergence from normal patterns of brain activity across time. This activity will be related to both antisaccade performance and to other measures of executive functioning (as measured by ODRT and WCST).

Hypothesis 2a: Schizophrenia and normal participants will show *dissimilar* patterns of brain activity associated with antisaccade performance across time. Data indicate that prefrontal cortex activity in normal participants decreases over time during the antisaccade task (Dyckman & McDowell, manuscript in preparation), but this pattern will oppose that seen in the schizophrenia participants, a group characterized by hypofrontality (Weinberger, et al., 1994). A previous fMRI study (Wexler, et al., 2000) investigating practice of a verbal working memory task reported increased activation in inferior frontal cortex with training. Thus, as schizophrenia participants' antisaccade performance improves over time, prefrontal BOLD signal will *increase* and will be greater in the schizophrenia group at Post-Test than Pre-Test.

Hypothesis 2b: Schizophrenia participants who show the greatest change in prefrontal cortex activity between Pre- and Post-Test will have the biggest decrease in antisaccade error rate and the biggest improvement on other measures of executive function as measured by ODRT and WCST. As such, it is predicted that schizophrenia participants with the greatest increase in prefrontal cortex activity with antisaccade practice (and concomitantly the fewest antisaccade errors) will improve more on ODRT and WCST. Specifically, they will show fewer delay period errors and improved accuracy during ODRT and fewer perseverative errors during WCST.

CHAPTER 3

METHODS

Participants

Twenty-seven participants diagnosed with DSM-IV schizophrenia (age: M = 38 years, SD = 11; 41% women; 3 left-handed) and twenty-eight healthy participants (age: M = 36 years, SD = 12; 46% women; 3 left-handed) were studied. Schizophrenia participants were recruited from regional mental health centers and through newspaper advertisements and flyers posted throughout the community. Schizophrenia participants were diagnosed with the Patient Edition of the Structured Clinical Interview for DSM-IV (First, Spitzer, & Gibbon, 1995) and rated with Scales for the Assessment of Negative Symptoms (SANS), Scales for the Assessment of Positive Symptoms (SAPS), and Global Assessment Functioning (GAF).

Healthy participants (matched by gender, age, and handedness) were recruited through newspaper advertisements, flyers posted throughout the community, through ads on www.craigslist.org, and from the Georgia Department of Labor. Healthy participants were interviewed with the Non-Patient Edition of the Structured Clinical Interview for DSM-IV-TR (First, et al., 1995) and screened with the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991).

All participants were free of serious physical health problems and absent of known neurological hard signs. Exclusion criteria included loss of consciousness for more than 30 min, history of severe head trauma or electroconvulsive therapy, and

current drug or alcohol abuse. Participants were also screened for contraindications for functional magnetic resonance imaging (fMRI) (i.e., eliminated for the following reasons, if: pregnant; are claustrophobic; have any of the following: hearing aid, pacemaker, shrapnel in eyes, skin, body, aortic clips, prosthesis, heart valve replacement, I.U.D., metal plates, pins, screws, or wires). All participants provided informed consent as per University of Georgia Institutional Review Board requirements and were paid for their time.

Procedure

Participants took part in a two-week trial (Table 3.1: "Study Schedule" below). Before the start of the two-week trial, participants completed two tests as baseline measurements of generalized executive control - WCST and ODRT. For the two-week trial, fMRI data were acquired on three occasions (Pre-Test, Mid-Test, Post-Test) while participants engaged in three different saccade tasks during each session (antisaccade-fixation (AF), prosaccade-fixation (PF), anti-/pro-saccade (AP)). Between fMRI sessions, participants practiced an assigned eye movement task each day while eye-tracker data were recorded. Thirteen schizophrenia participants and thirteen healthy participants practiced the antisaccade task, and fourteen schizophrenia participants and fifteen healthy participants practiced the prosaccade task. At the end of the two-week trial, participants repeated WCST and ODRT.

<u>WCST and ODRT Sessions</u>

WCST

Participants were administered the WCST Computer Version (Version 4.21.020, Psychological Assessment Resources, Inc., Lutz, Florida, USA) using standardized

instructions (Heaton, 1981). Stimuli were displayed approximately 70cm in front of the participant on a ViewSonic PF790 CRT monitor (Pentium IV, 1700MHz). Participants were instructed to match "response cards" appearing at the bottom of the screen to one of four "key cards" appearing at the top of the screen (see Figure 3.1). Cards were matched according to three different dimensions – color, form or number. Participants, however, were not instructed on how to match the cards. Participants sorted response cards until they matched six categories or until all 128 cards were sorted. After 10 consecutive correct cards were sorted, a new sorting principle was instituted without warning. There was no time limit on the test.

In order to match the cards, participants used a computer mouse to select the key card that matched the response card. Once the selection was made, the response card moved under the selected key card, and participants received visual and auditory feedback of their selection – "RIGHT" or "WRONG". If the participant, however, decided to change their answer before the response card stopped moving (2.5 sec), they were instructed to click the mouse again and the response card would return to its original location at the bottom of the screen, at which point they could make another selection. After feedback, participants were instructed to simply continue matching the cards correctly or, if wrong, to try to match the next card correctly and then to continue matching the cards correctly until the test was over.

ODRT

Eye movements for the ODRT were recorded using one of two systems: 1) an Eye Trak model 310 eye movement monitor with infrared sensors mounted onto a headband (Applied Science Laboratories, Waltham, Massachusetts, USA) or 2) an EyeLink II eye

movement monitor with infrared cameras mounted onto a headband (SR Research Ltd., Ottawa, Ontario, Canada).

Participants were seated 70 cm from a color flat screen monitor in a quiet darkened room. A chin rest was used to minimize head movement during the task. Eye movement recordings were digitized at 500 Hz and displayed on a computer monitor, and performance could therefore be monitored continuously by the experimenter. Prior to each task participants were presented with calibration targets at central fixation, ±5º, 10º, and 15º.

Participants were instructed to keep their eyes on a centrally presented cross for its duration. After 1250 or 1750 msec (pseudorandomized ITI) a 1º blue dot was presented (100 msec) at one of four pseudorandomly selected peripheral locations (± 8º or 16º). Participants were instructed to remember the location of the peripheral cue while keeping their eyes fixated on the central cross. After a delay period (4000 msec) the fixation cross was turned off, signaling the participant to move their eyes to the remembered location as quickly and accurately as possible. After 1500 msec of response time, a 1º pink dot appeared in the correct location (500 msec) to reinforce the accuracy component of the task. Forty trials were presented sequentially for a total run time of 4 min 56 sec (see Figure 3.2).

FMRI Sessions

Brain imaging was performed at the Bio-Imaging Research Center at the University of Georgia with a GE Excite HD 3.0T MRI scanner (Milwaukee, Wisconsin). Immediately before entering the scanner for the first time, participants viewed the practice stimuli and were given task instructions. During imaging, participants were

provided with earplugs and positioned in a supine position. Their heads were stabilized with foam padding and head restraints. A dual mirror box was placed 16 cm above and in front of the participant's eyes, designed to make stimuli visible to the participant and the participant's eyes visible to an eye-tracking camera. Eye movements were recorded with MRI compatible equipment (MEyeTrack LR, SensoMotoric Instruments, Inc., Berlin, Germany). The eye was illuminated via an infrared light source, and the eye image was relayed via a remote infrared camera with long-range optics. Eye movements were displayed on a computer monitor so performance could be monitored and recorded continuously (sampling rate = 60 Hz) for later analysis. An LCD Projector (NEC Viewtechnology, Ltd., Tokyo, Japan) displayed stimuli onto a rear projection screen standing 174 cm from the participant's nasion. Stimulus presentation was controlled with Presentation software (Neurobehavioral Systems, Albany, California).

After positioning participants in the scanner and prior to the acquisition of MRI data, a parallel imaging calibration (ASSET, FOV = 30cm, slice thickness 6.0mm, 31 slices, scan time 6 sec) was run to provide a coarse measurement of the magnetic field in the presence of the participant. After the calibration, a rapid three-dimensional T1-weighted structural MRI scan of high resolution was collected (BRAVO protocol: ASSET factor =2, echo time [TE] = 4.6 msec, repetition time [TR] = 10.8 msec, flip angle = 13°, number of excitations [NEX] = 0.5, matrix = 352 × 224, field of view [FOV] = 24 cm [resulting in an in-plane resolution of 0.68 × 1.07], slice thickness of 1.2 mm, frequency direction A/P, 150 slices, scan time 3 min 7 sec, bandwidth = 25 kHz, phase FOV = 1, time to inversion [prep time] = 450ms) for definition of the oblique plane (the line connecting the superior edge of the anterior commissure and the inferior edge of the

posterior commissure). Following the structural scan, an eye-calibration trial was run to ensure eye tracking data quality. Three functional runs were then conducted. For each, a series of T2*-weighted functional images were obtained (oblique prescription, gradient echo echo-planar imaging pulse sequence [EPI] with data points in k-space sampled line by line: matrix = 64 × 64, FOV = 22 cm [resulting in an in-plane resolution of 3.4375 × 3.4375], slice thickness of 4mm, TE = 30 msec, TR = 2000 msec with a single-shot interleave, flip angle = 90°, 33 slices, scan time 6 min 12 secs, frequency direction R/L, bandwidth = 250 kHz, phase FOV = 1, NEX = 1, ramp-sampling turned on, ASSET (acceleration factory) = 2.0 Ph).

Brain coverage for functional scans was defined by placing the most superior scan plane tangent to the highest point of the somatosensory cortex and parallel to the oblique plane. Prior to each run, participants were reminded of specific task instructions (PF, AF, or AP). Each functional run began with four null repetitions (not included in the analysis) to allow the magnetization to stabilize at steady state equilibrium. After the three functional runs, a fourth EPI sequence (same parameters except total scan time = 28 sec) was acquired axially (non-oblique) while the participant was at rest. The purpose of the axial EPI images was to provide a coordinate template to which the oblique EPI images would be registered. Finally, a three-dimensional T1-weighted structural MRI scan of high-resolution for definition of anatomical structures within each brain was acquired (fast spoiled gradient echo [FSPGR] protocol; TE = Min-Full, TR = 7.8 msec, flip angle = 20°, NEX = 1, matrix = 256 × 256, FOV = 24 cm [resulting in an in-plane resolution of 0.9375 × 0.9375], slice thickness of 1.2 mm, frequency direction A/P,

150 slices, scan time 6 min 20 sec, bandwidth = 31.25 kHz, phase FOV = 0.7, prep time 450 msec).

Block designs were used for each functional run because 1) they optimize contrast to noise ratio (Bandettini & Cox, 2000), and 2) previous studies in the authors' lab have demonstrated the successful use of this method to evaluate whole brain activations associated with basic saccade-related neural substrates (e.g., Camchong, Dyckman, Austin, Clementz, & McDowell, 2008; Camchong, et al., 2006; Dyckman, Camchong, Clementz, & McDowell, 2007; McDowell, et al., 2002). Each run consisted of 13 alternating blocks of a baseline and an experimental condition. The prosaccade/fixation run alternated between blocks of fixation and blocks of 7 prosaccade trials. The antisaccade/fixation run alternated between blocks of fixation and blocks of 7 antisaccade trials. The antisaccade/prosaccade run alternated between blocks of 7 prosaccade trials and blocks of 7 antisaccade trials. The order of the runs was counterbalanced across participants.

Practice Sessions

In the lab, participants completed three practice runs per day over two weeks. The prosaccade practice group completed three runs of alternating blocks of fixation and prosaccades, identical to the prosaccade/fixation run described above but with a jittered inter-trial interval (ITI). The antisaccade practice group completed three runs of alternating blocks of fixation and antisaccades, identical to the antisaccade/fixation run described above but also with a jittered ITI. Participants received a short break after each run. All participants completed 126 saccade trials per day. Practice session eyetrack data

were recorded using the same eye movement monitoring systems and with identical procedures as those described for the ODRT (see above: WCST and ODRT Sessions).

Stimuli

WCST Stimuli

See Figure 3.1.

ODRT Stimuli

See Figure 3.2.

FMRI Stimuli

Visual stimuli consisted of three different block design tasks – prosaccade/fixation (see Figure 3.3), antisaccade/fixation (see Figure 3.4), and antisaccade/prosaccade (see Figure 3.5). The gap versions of the saccade tasks were used to avoid a ceiling effect on percentage of correct antisaccade responses, which would prohibit practice-related improvement from being observed as participants make a larger number of errors on antisaccade tasks when a gap exists (e.g., Fischer, et al., 2000; McDowell & Clementz, 1997).

Fixation Block

A 2.5° pink dot was presented at central fixation for 28.0 seconds. The participant was instructed to fixate on the dot as it remained in the center of the screen.

Prosaccade Block

A 2.5° yellow dot was presented at central fixation to start the trial and remained there for 2400 msec. The center stimulus was extinguished, and 200 msec later (gap), a 2.5° yellow dot was presented was presented ±8º or 16º from fixation in the horizontal plane for 1400 msec (half in each visual field). Participants were instructed to move their eyes to the dot as quickly and accurately as possible. Each prosaccade block (28.0 sec) consisted of 7 prosaccade trials.

Antisaccade Block

The stimuli and timing for the antisaccade task were identical to those for the prosaccade task except that the dot was blue to signal an antisaccade trial. Participants were instructed to move their eyes to the *mirror image* location of the dot as quickly and accurately as possible without looking at the cue itself. Each antisaccade block (28.0 sec) consisted of 7 antisaccade trials.

Practice Session Stimuli

Visual stimuli for practice sessions were identical to those described for the fMRI sessions with one exception – at the beginning of each trial, the cue for central fixation was pseudorandomly jittered between 2150 and 2650 msec.

Analysis

WCST Data

Primary variables of interest were those associated with general conceptual and problem solving abilities (i.e. percent perseverative responses, percent perseverative errors, categories completed (Paolo, Troster, Axelrod, & Koller, 1995)), impairments on which have been reported in previous studies of the WCST in schizophrenia (Berman, et al., 1995; Berman, Zec, & Weinberger, 1986). A *perseverative response* was when a participant persisted in responding to a stimulus characteristic (i.e., color, form, or number) that was incorrect; responses that matched the perseverated-to principle were scored as perseverative regardless of whether they were correct or incorrect. *Percent perseverative responses* reflects the density or concentration of perseverative responses in relation to overall test performance. It is computed by calculating the ratio of perseverative responses to the number of trials administered. The resulting fraction is then multiplied by 100 and rounded to the nearest whole number. A preservative error was when a participant persisted in responding to a stimulus characteristic (i.e., color, form, or number) that was incorrect *and* the response was also incorrect. *Percent perseverative errors* reflects the density or concentration of preservative errors in relation to overall test performance. It is computed by calculating the ratio of perseverative errors to the number of trials administered. The resulting fraction is then multiplied by 100 and rounded to the nearest whole number. The number of *categories completed* is simply the number of categories (i.e., each sequence of 10 consecutive correct matches to the criterion sorting category) that the participant successfully completed during the test. Scores can range from a minimum of 0 to a maximum of 6.

Eye Movement Data

Eye movement data from the ODRT, fMRI, and practice sessions were scored using programs written in MATLAB (The Mathworks Inc., Natick, MA). Trials with blinks in the pre-saccade period (from 350 msec prior to stimulus until saccade onset) and trials with no saccades were eliminated. Saccades from each session were scored for correct or incorrect direction, and latency and spatial accuracy to correct saccades.

First, the percentage of errors generated during trials was calculated ([number of trials with at least one error saccade/total number of usable trials] × 100). For antisaccade trials an error saccade was an initial glance toward (instead of away from) the cue. For ODRT trials an error saccade was an initial glance toward the peripheral cue during its presentation or anytime during the remainder of the delay period. Second, the latencies of correct saccades were calculated (time in milliseconds between the cue presentation and the start of the saccade [>90 msec]). Third, the accuracy of correct saccades was determined (initial saccade amplitude/cue amplitude; 1.00 indicates perfect accuracy).

FMRI Data

For the current paper, only the antisaccade-fixation imaging data were analyzed. Analyses were conducted using Analysis of Functional NeuroImages (AFNI) (Cox, 1996) software with methods similar to those previously published (Camchong, et al., 2006; Dyckman, et al., 2007). Three-dimensional datasets were created from individual image files. For each run, volumes were time corrected for slice acquisition order and then registered to a representative volume to correct for minor head movement over time (3dvolreg). A 4-mm full-width at half-maximum (FWHM) Gaussian filter was then

applied to each dataset. For each voxel, the percent change in BOLD signal from baseline was calculated for each of the 182 time points. Images from the second and third fMRI sessions were aligned with the images from the first fMRI session for more accurate comparisons across scanning sessions.

A hybrid independent component analysis (ICA) was then performed, similar to the approach described by McKeown (2000). This approach uses ICA to derive a set of task-related data-driven regressors that can be used to create a reference function for use in a GLM analysis (McKeown, 2000). Each individual subject's data was transformed into standardized space (based on Talairach & Tournoux, 1988), and an average dataset for each timepoint was created. Averaging across subjects is one alternative when estimating component maps using ICA. With a large number of subjects, as in the current study, it reduces the computational load, and still accurately estimates associated time courses, which can be used in a GLM analysis (Schmithorst & Holland, 2004). For antisaccade-fixation run, the three averages (one for each timepoint), were concatenated in space, and Probabilistic ICA (PICA) was performed using MELODIC (Beckmann & Smith, 2004). PICA yielded 42 spatially independent components, the first eight of which had time courses with the same peak frequency as our experimental design. Components 1, 2, and 4 were most associated with the pre-test session, components 3 and 5 were most associated with the mid-test session, and components 6, 7, and 8 were most associated with the post-test session. See Figures 4.40.1-3.

For each subject, for each timepoint, the percent signal change across time was correlated with the first eight PICA components. Of the remaining 34 components, 10 were associated with activity outside of the brain, so only 24 components were used as

artifact and/or motion regressors. Collapsing across the three timepoints, a one-sample t-test versus 0 was conducted to determine which areas of the brain showed BOLD signal change related to the experimental task for the antisaccade-fixation run. 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 5.7 mm) was applied to the t-map (Ward, 2000). Based on these simulations, the family-wise alpha of 0.05 was preserved with an a priori voxelwise probability of 0.025 and three-dimensional clusters with a minimum volume of 1088 µl (17 or more voxels). The resulting clustered t-map was used to identify regional BOLD signal changes.

The nature of the relationship between timepoints in the brain regions with significant activity was examined via a region of interest (ROI) analysis. ROIs were determined based on BOLD activations observed in the present data and fMRI studies of saccadic performance that demonstrate characteristic activations across a variety of cognitively simple and complex tasks (Dyckman, et al., 2007; Sweeney, et al., 2007). For each ROI, a sphere (radius 8 mm) was positioned at the center of mass of each region that showed a significant effect. Mean percent signal changes for each run were calculated for each ROI for each individual. Finally, for each ROI, a 2×2×2×3 repated-measures analysis of variance (ANOVA) was used to evaluate effects of diagnosis (normal, schizophrenia), practice group (pro-, anti-saccades), laterality (left, right), and timepoint (pre-, mid-, and post-test).

Specific Methodology

Below the Specific Aims are presented verbatim, followed by a restatement of hypotheses (edited to conserve space) and a summary of the critical methodology.

Specific Aim 1

Among schizophrenia participants, behavioral performance following practice will show patterns similar to that documented in normal participants.

Hypotheses 1a and 1b state that schizophrenia participants (like normal participants) will show increased performance following task-consistent practice on saccade tasks, although antisaccade performance, especially, may be characterized by less extensive and less rapid improvement.

Participants: 27 schizophrenia and 28 normal participants.

Data: Behavioral data from a) the laboratory practice sessions (PS #1-8), and b) the fMRI test sessions (Pre-, Mid-, and Post-Test). The practice and test data are expected to result in similar patterns; antisaccade-practicers will improve performance and on antisaccades (increased percent of correct trials) and prosaccade-practicers will improve performance on prosaccades (decreased latencies). The increased number of available data points from practice sessions (8 versus 3), however, may be optimal for determining between-group differences in rate of change, which will be estimated by a best-fit binomial function. *Dependent variables*: Antisaccade error rates, and pro- and anti-saccade latencies for a) practice sessions, and b) test sessions.

Analyses: A 2x2x8 and 2x2x3 repeated measures ANOVA with between-subjects factors of group (normal, schizophrenia) and practice task (pro-, anti-saccades), and

within-subjects factors of a) practice session (PS #1-8), and b) test session (Pre-, Mid-, Post-Test) will be conducted. When appropriate, Hyundt-Feldt adjusted degrees of freedom will be used and Helmert contrasts will determine differences between levels (similar to (Dyckman & McDowell, 2005)). Effect sizes will be calculated for significant between group variables.

Results: These hypotheses evaluate the effects and rate of task-consistent practice. Improved performance would be decreased anti-saccade errors (with preserved or decreased latencies). Decreased errors within the context of increased latencies may indicate a speed/accuracy trade off indicative of changed strategies, but not necessarily of improved performance. Decreased rate of change in antisaccade error rate would be indicated by a shallower slope among the schizophrenia participants (in the face of a lower y-intercept).

Hypothesis 1c states that schizophrenia (like normal) participants will make more antisaccade errors following prosaccade practice, and they may be more susceptible to this manipulation than normal participants.

Participants: 27 schizophrenia and 28 normal participants.

Data: Behavioral data from the fMRI testing sessions (Pre-, Mid-, Post-Test). Practice data cannot be used because participants are never exposed to the non-practiced trial types (i.e. prosaccade practice participants never experience antisaccade tasks in the laboratory). *Dependent variables*: Antisaccade error rates, and pro- and anti-saccade latencies.

Analyses: A 2x2x3 repeated measures ANOVA conducted with between-subjects factors of group (normal, schizophrenia) and practice task (pro-, anti-saccades), and

within-subjects factor of test session (Pre-, Mid-, Post-Test). Hyundt-Feldt adjusted degrees of freedom will be used and Helmert contrasts will determine differences between levels.

Results: This hypothesis evaluates the effects of *task-inconsistent* practice. Decreased performance would be increased antisaccade errors or increased latencies (pro- or anti-saccades).

Specific Aim 2

Among antisaccade-practiced schizophrenia participants, there will be a divergence from normal patterns of brain activity that is accentuated across time and that is related to both antisaccade task performance and to executive function (as measured by ODRT and WCST).

Hypothesis 2a states that schizophrenia and normal participants will show dissimilar patterns of brain activity change associated with antisaccade performance across time.

Participants: 13 schizophrenia and 13 normal participants who practice antisaccades.

Data: ROI fMR imaging data

Analyses: A 2x3 repeated measures ANOVA with between-subjects factor of group (normal, schizophrenia) and within-subjects factor of test session (Pre-, Mid-, Post-Test). To determine the origin and direction of BOLD signal changes apparent in the repeated measures analysis, t-tests (versus 0) will be conducted. *Dependent variable*: ROI BOLD signal.

Results: At Pre-Test whole brain analyses are expected to demonstrate that all participants show activity in basic saccade-related regions (e.g. FEF, SEF, PPC) but that schizophrenia participants show a general dampening of signal (Camchong, et al., 2008), particularly apparent in striatum (Raemaekers, et al., 2002) and PFC (McDowell, et al., 2002). Across test sessions, however, a differential pattern is expected to arise. Data from normal participants demonstrates both increased signal in posterior cingulate and decreased signal in PFC during anti-saccade performance (Dykman & McDowell, manuscript in preparation). Because the increased posterior cingulate activity was observed following practice for both pro- and anti-saccades, and schizophrenia participants show normal prosaccade performance, schizophrenia participants may also show practice-associated increases in this area. As schizophrenia participants' antisaccade performance improves across time, however, the PFC BOLD signal will *increase* so that by the Post-Test it will be greater than that observed in normal participants.

Hypothesis 2b states that schizophrenia participants who show the greatest PFC change between Pre- and Post-Test will show the greatest improvement in executive functioning, as measured by improved antisaccade error rates, improved spatial accuracy during ODRT and fewer perseverative errors during WCST.

Participants: 27 schizophrenia participants.

Data: a) Brain imaging data for the PFC ROI across test sessions (Pre-, Mid-, Post-Test), as well as changes in b) antisaccade error rates, c) ODRT memory-saccade accuracies, and d) WCST perseverative error rates. *Dependent variables*: PFC ROI

BOLD signal, antisaccade error rates, memory-guided saccade accuracies, perseverative WCST errors.

Analyses: First, the PFC ROI BOLD signal change will be analyzed with a 2x3 repeated measures ANOVA with between-subjects factor of group (normal, schizophrenia) and within-subjects factor of test session (Pre-, Mid-, Post-Test). To determine the origin and direction of BOLD signal changes resulting from the repeated measures analysis, t-tests (versus 0) will be conducted. Second, the correlation coefficients from the PFC ROI at the Post-Test will be correlated with three forms of behavioral data; 1) antisaccade error rates during the test sessions (because images were acquired while participants were engaged in the behavior, making it the most closely-related data set), 2) ODRT memory-guided saccade accuracy, and 3) perseverative WCST errors.

Results: Practice-induced improvement on antisaccades may reflect a reversal of the well-documented hypofrontality among schizophrenia participants.

Table 3.1

Study Schedule.

	Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 1				WCST #1 ODR #1	FMRI #1 (Pre-Test)	Practice Session #1	
Week 2		Practice Session #2	Practice Session #3	Practice Session #4	FMRI #2 (Mid-Test)	Practice Session #5	
Week 3		Practice Session #6	Practice Session #7	Practice Session #8	FMRI #3 (Post-Test)	WCST #2 ODR #2	

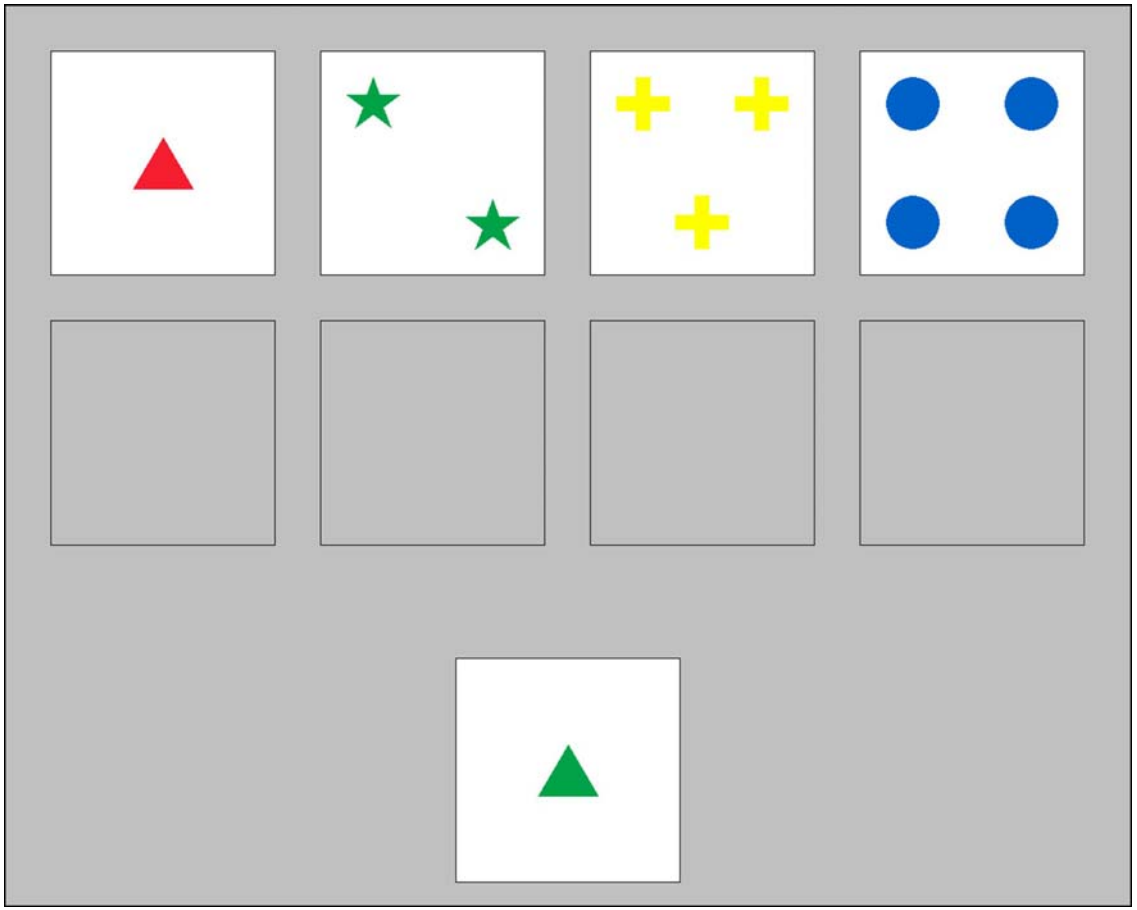


Figure 3.1 WCST

Stimuli used for WCST. Participants were instructed to match the response card (bottom of screen) to one of the four key cards (top of the screen). Cards were sorted by one of three sorting principles: 1) color, 2) form, or 3) number.

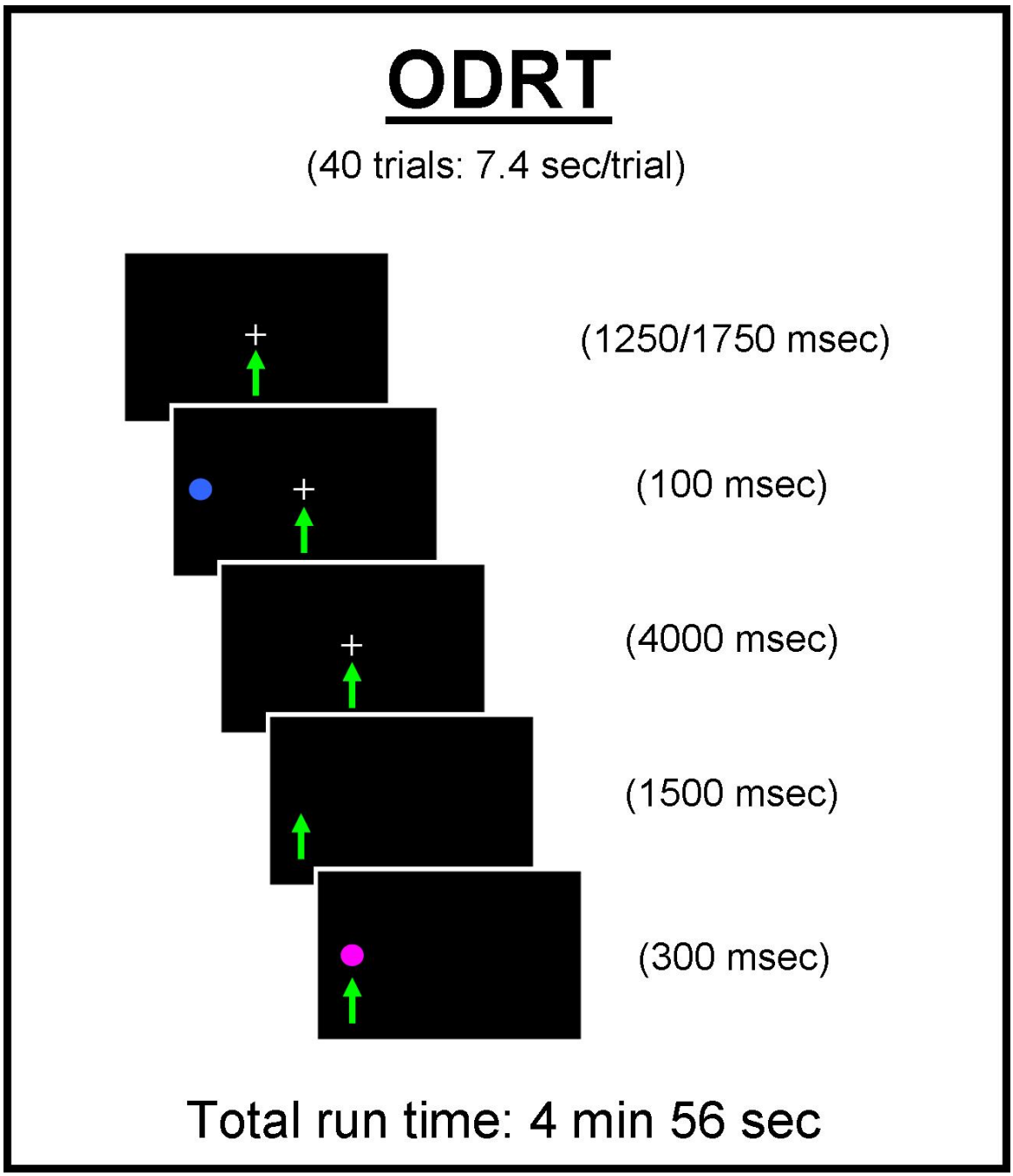


Figure 3.2 ODRT

Stimuli used for ODRT. Participants were instructed to keep their eyes on the centrally presented cross for its durations and then to move their eyes as quickly and accurately as possible to the remembered location of the peripheral cue (blue dot). The arrow indicates where the participant should be looking at each point in time. The ODRT consisted of 40 trials.

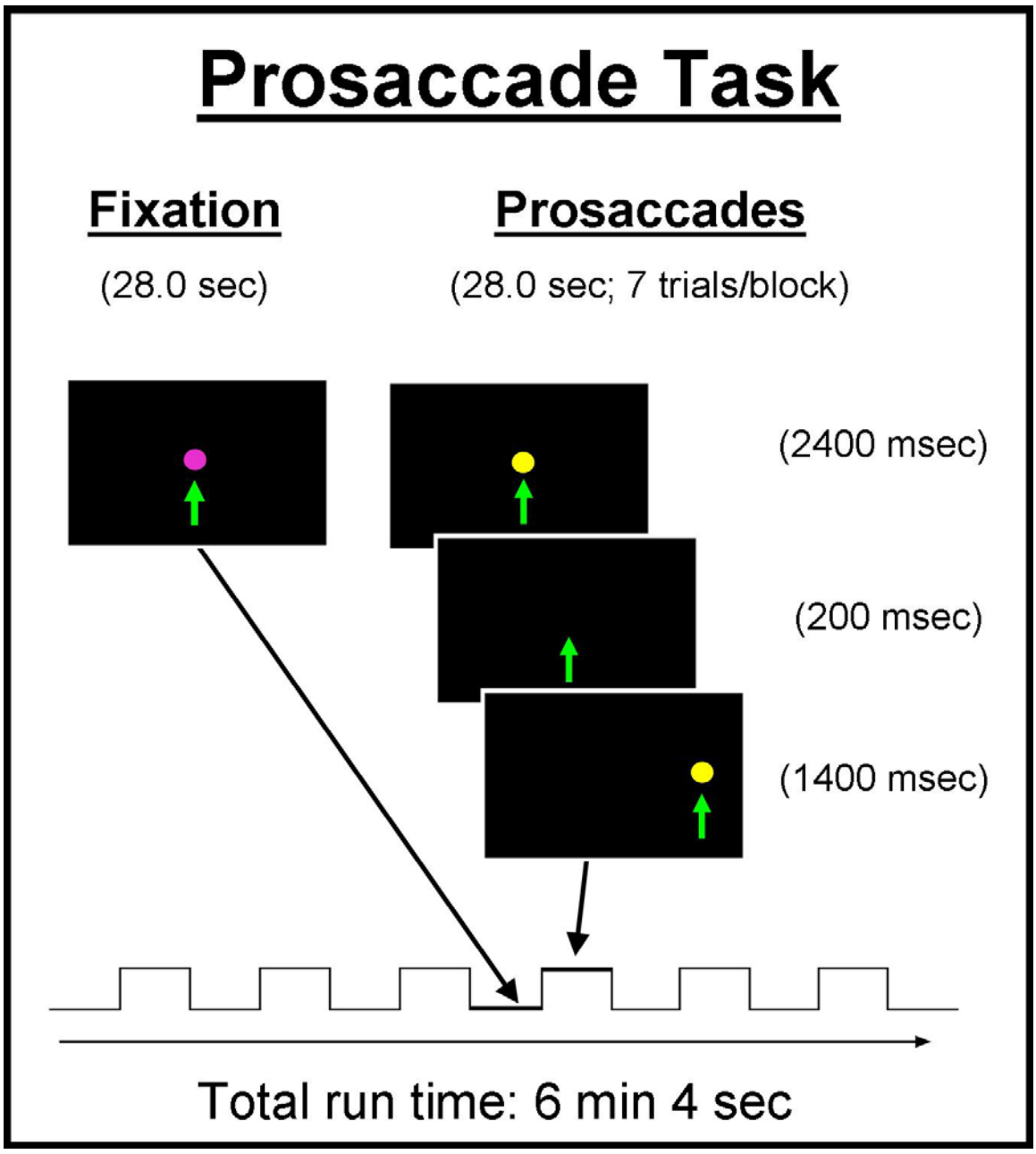


Figure 3.3 Prosaccade/Fixation Task

Stimuli used for prosaccade/fixation task. Participants were instructed to fixate on the pink dot and then to follow the yellow dot with their eyes quickly and accurately as possible. The arrow indicates where the participant should be looking at each point in time. The prosaccade task consisted of 42 trials.

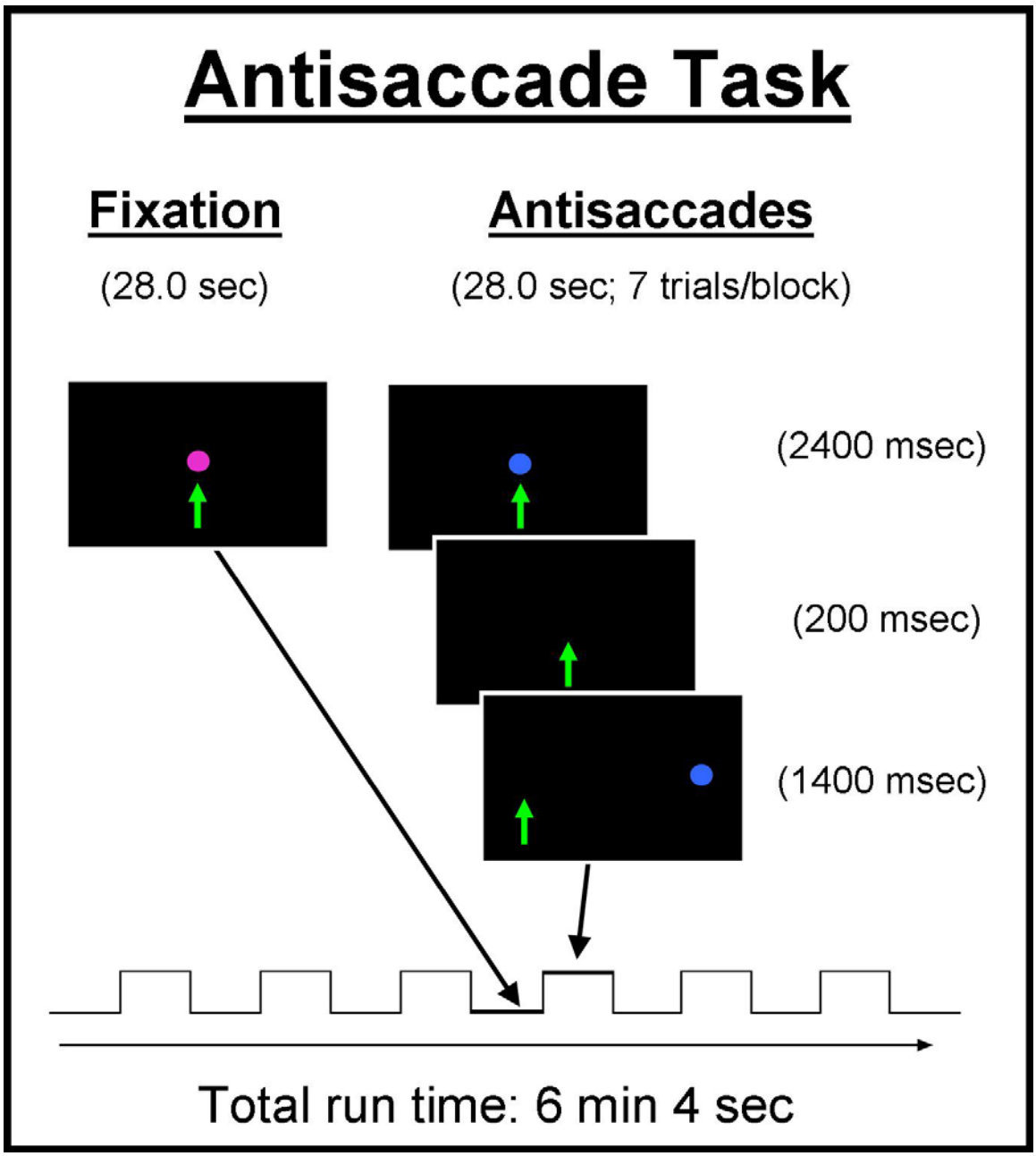


Figure 3.4 Antisaccade/Fixation Task

Stimuli used for antisaccade/fixation task. Participants were instructed to fixate on the pink dot and to look at the blue dot when it was in the middle. When the blue dot moved to the left or right of fixation, participants were instructed to move their eyes to the mirror image location of the peripheral cue as quickly and accurately as possible without looking at the cue itself. The arrow indicates where the participant should be looking at each point in time. The antisaccade task consisted of 42 trials.

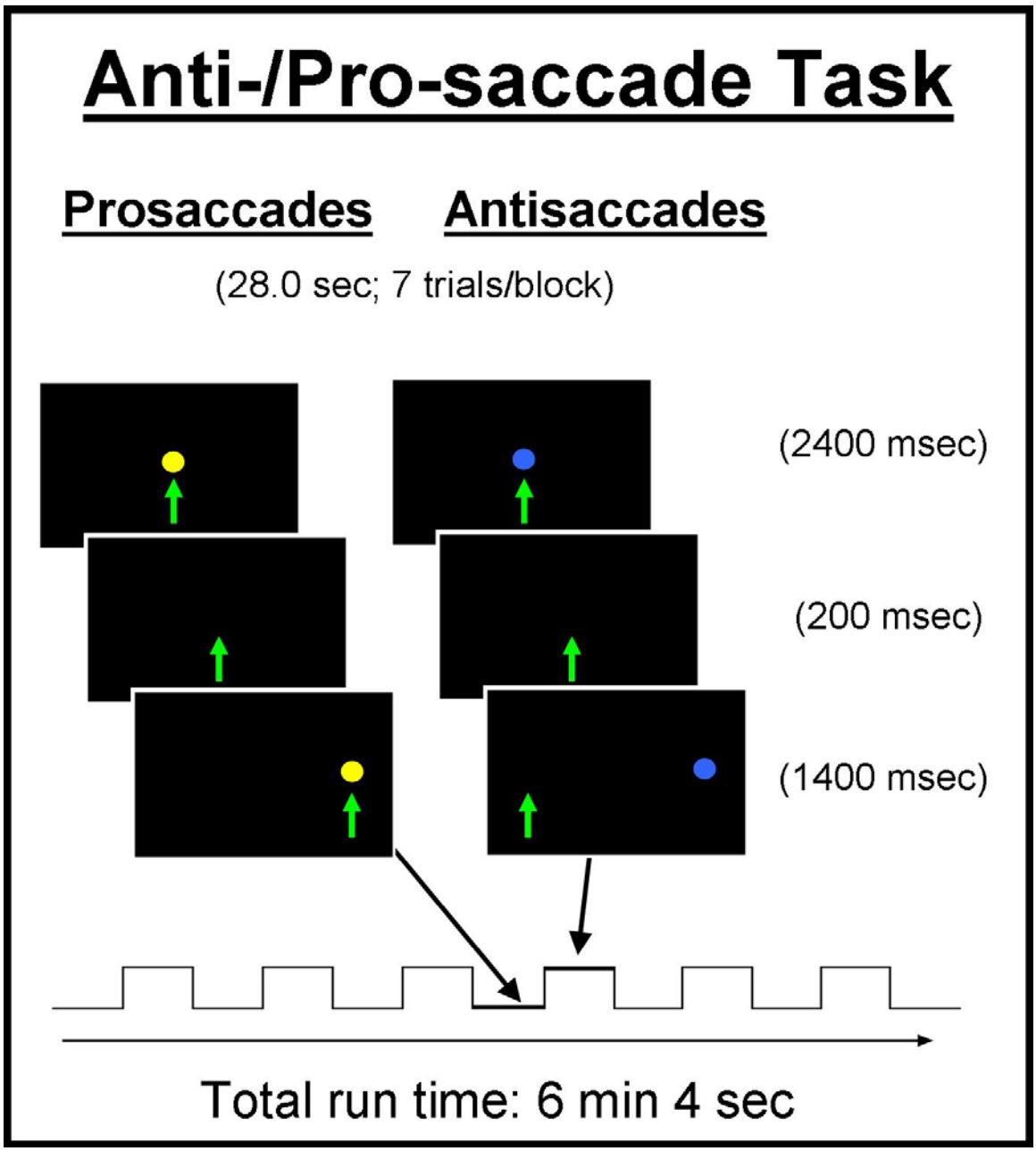


Figure 3.5 Antisaccade/Prosaccade Task

Stimuli used for antisaccade/prosaccade task. Participants were given instructions identical to those specified in Figures 3.2 and 3.3 above. The arrow indicates where the participant should be looking at each point in time. The prosaccade task consisted of 49 trials; the antisaccade task consisted of 42 trials.

CHAPTER 4

RESULTS

WCST Data

The data collected during the WCST task were analyzed using a 2 x 2 x 2 ANOVA (diagnosis x practice group x timepoint) with diagnosis and practice group being between-subjects factors and timepoint entered as a within-subjects factor.

Number of Trials Administered

Analysis of number of trials administered revealed a significant effect of time [$F(1,49) = 20.691$, $p < 0.001$], demonstrated as fewer number of trials at post-test ($M = 93.0$, $SE = 2.25$) compared to pre-test ($M = 105.0$, $SE = 2.86$). There was also a significant effect of diagnosis [$F(1,49) = 15.197$, $p < 0.001$], demonstrated as fewer number of trials for the normal group ($M = 89.7$, $SE = 3.46$) compared to the schizophrenia group ($M = 108.2$, $SE = 3.25$). For number of WCST trials administered, there was no significant effect of practice group, and there were no interactions. See Figure 4.1.

Errors

Analysis of WCST percent of errors revealed a significant effect of time [$F(1,49) = 20.691$, $p = 0.001$], demonstrated as fewer errors at post-test ($M = 23.36\%$, $SE = 2.32$) compared to pre-test ($M = 29.35\%$, $SE = 2.24$). There was also a significant effect of diagnosis [$F(1,49) = 11.849$, $p = 0.001$], demonstrated as fewer errors for the normal

group (M = 19.11%, SE = 3.06) compared to the schizophrenia group (M = 33.60%, SE = 2.88). For WCST percent of errors, there was no significant effect of practice group, and there were no interactions. See Figure 4.2.

Perseverative Errors

Analysis of WCST percent of perseverative errors revealed a significant effect of diagnosis [F(1,49) = 7.217, p = 0.010], demonstrated as fewer perseverative errors for the normal group (M = 10.19%, SE = 2.70) compared to the schizophrenia group (M = 20.16%, SE = 2.54). For WCST percent of perseverative errors, there was no significant effect of time or practice group, and there were no interactions. See Figure 4.3.

Conceptual Level Responses

Analysis of WCST percent of conceptual level responses (CLR) revealed a significant effect of time [F(1,49) = 10.482, p = 0.002], demonstrated as a greater percent of CLR at post-test (M = 70.68%, SE = 3.09) compared to pre-test (M = 62.36%, SE = 2.90). There was also a significant effect of diagnosis [F(1,49) = 13.123, p = 0.001], demonstrated as a greater percent of CLR for the normal group (M = 76.55%, SE = 3.97) compared to the schizophrenia group (M = 56.76%, SE = 3.74). For WCST percent of conceptual level responses, there was no significant effect of practice group, and there were no interactions. See Figure 4.4.

Perseverative Responses

Analysis of WCST percent of perseverative responses revealed a significant effect of diagnosis [F(1,49) = 6.648, p = 0.013], demonstrated as fewer perseverative responses for the normal group (M = 11.06%, SE = 3.67) compared to the schizophrenia group (M

= 24.06%, SE = 3.45). Post-hoc independent samples t-tests were used to further identify diagnosis group-related influences on WCST performance. Further analyses confirmed a significant difference between diagnosis groups at post-test [t(51) = -2.705, p = 0.009], demonstrated as fewer perseverative responses for the normal group (M = 8.60%, SD = 4.97) relative to the schizophrenia group (M = 24.14%, SD = 28.30). Analyses also revealed a marginally significant difference between diagnosis groups at pre-test [t(51) = -1.935, p = 0.058], demonstrated as fewer perseverative responses for the normal group (M = 13.52%, SD = 10.43) relative to the schizophrenia group (M = 23.10%, SD = 23.10). Paired samples tests were used to further identify time-related influences on WCST performance. Among all subjects, there was not a significant difference in percent perseverative responses between pre-test to post-test [t(52) = 1.009, p = 0.318]. In the normal group, there was a significant change in performance from pre-test to post-test [t(24) = 2.143, p = 0.042], demonstrated as decreased percent of perseverative responses at post-test (M = 8.60%, SD = 4.97) compared to pre-test (M = 13.52%, SD = 10.43). In the schizophrenia group, however, the change in percent of perseverative responses from pre-test to post-test was not significant (p = 0.687). For WCST percent of perseverative responses, there was no significant effect of practice group, and there were no other interactions. See Figure 4.5.

Non-Perseverative Errors

Analysis of WCST percent of non-perseverative errors (NPE) revealed a significant effect of time [F(1,49) = 12.253, p = 0.001], demonstrated as a fewer NPE at post-test (M = 9.31%, SE = 1.03) compared to pre-test (M = 13.10%, SE = 1.13). There was also a significant effect of diagnosis [F(1,49) = 6.136, p = 0.017], demonstrated as

fewer NPE for the normal group (M = 8.89%, SE = 1.37) compared to the schizophrenia group (M = 13.58%, SE = 1.29). For WCST percent of NPE, there was no significant effect of practice group, and there were no interactions. See Figure 4.6.

Categories Completed

Analysis of WCST number of categories completed revealed a significant effect of diagnosis [F(1,49) = 9.183, p = 0.004], demonstrated as a greater number of categories completed for the normal group (M = 5.63%, SE = 0.33) compared to the schizophrenia group (M = 4.22%, SE = 0.31). For WCST number of categories completed, there was no significant effect of time or practice group, and there were no interactions. See Figure 4.7.

Trials to Complete First Category

Analysis of WCST number of trials to complete the first category revealed a significant effect of diagnosis [F(1,49) = 6.050, p = 0.017], demonstrated as a fewer number of trials for the normal group (M = 15.7, SE = 5.3) compared to the schizophrenia group (M = 33.7, SE = 5.0). For WCST number of trials to complete the first category, there was no significant effect of time or practice group, and there were no interactions. See Figure 4.8.

ODRT Data

The eyetrack data collected during the ODR task were analyzed using a 2 x 2 x 2 ANOVA (diagnosis x practice group x timepoint) with diagnosis and practice group being between-subjects factors and timepoint entered as a within-subjects factor.

Anticipatory Saccades

Analysis of number of anticipatory saccades revealed a significant effect of time [$F(1,54) = 9.047$, $p = 0.004$], but no time by diagnosis interaction ($p = 0.094$). Post-hoc independent samples t-tests were used to further identify diagnosis-related influences on ODR performance. Further analyses confirmed a marginally significant difference between diagnosis groups at post-test [$t(56) = -1.905$, $p = 0.062$], demonstrated as fewer anticipatory saccades for the normal group ($M = 6.96$, $SD = 5.55$) relative to the schizophrenia group ($M = 10.83$, $SD = 9.31$). The group difference at pre-test was not significant ($p=0.931$). Paired samples tests were used to further identify time-related influences on ODR performance. Among all subjects, there was a significant difference in number of anticipatory saccades between pre-test to post-test [$t(57) = 2.846$, $p = 0.006$] demonstrated as fewer anticipatory saccades at post-test ($M = 8.96$, $SD = 7.90$) compared to pre-test ($M = 12.17$, $SD = 8.47$). In the normal group, there was a significant change in performance from pre-test to post-test [$t(27) = 2.786$, $p = 0.010$], demonstrated by fewer anticipatory saccades at post-test ($M = 6.96$, $SD = 5.55$) compared to pre-test ($M = 12.07$, $SD = 10.2$). In the schizophrenia group, however, the decrease in number of anticipatory saccades from pre-test ($M = 12.26$, $SD = 6.64$) to post-test ($M = 10.83$, $SD = 9.31$) was not significant ($p = 0.3$). For number of anticipatory saccades, there was no significant effect of practice group or diagnosis, and there were no other interactions. See Figure 4.9.

Average Anticipatory Saccades Per Trial

Analysis of average number of anticipatory saccades per trail revealed a marginally significant effect of time [$F(1,54) = 3.367$, $p = 0.072$], demonstrated as fewer

anticipatory saccades at post-test (M = 0.446, SE = 0.108) compared to pre-test (M = 0.693, SE = 0.118). For average number of anticipatory saccades per trial, there was no significant effect of practice group or diagnosis, and there were no interactions. See Figure 4.10.

Percent Correct

Analysis of percent correct of ODR revealed a significant effect of time [$F(1,54) = 13.973$, $p < 0.001$], a marginally significant effect of diagnosis [$F(1,54) = 3.308$, $p = 0.074$], and a marginally significant time by practice group interaction [$F(1,54) = 3.896$, $p = 0.054$]. Post-hoc independent samples t-tests were used to further identify diagnosis group-related influences on ODR performance. Further analyses confirmed a significant difference between diagnosis groups at post-test [$t(56) = 2.249$, $p = 0.028$], demonstrated as higher percent correct for the normal group (M = 83.8%, SD = 11.3) relative to the schizophrenia group (M = 73.8%, SD = 20.7). The group difference at pre-test was not significant ($p=0.271$). Post-hoc independent samples t-tests were also used to further identify practice group-related influences on ODR performance, but further analyses determined that practice groups effects were insignificant at both pre-test ($p = 0.456$) and post-test ($p = 0.260$). Paired samples tests were used to further identify time-related influences on ODR performance. Among all subjects, there was a significant difference in percent correct between pre-test to post-test [$t(57) = -3.593$, $p = 0.001$] demonstrated as increased percent correct at post-test (M = 78.69, SD = 17.45) compared to pre-test (M = 70.18, SD = 19.94). In the antisaccade practice group, there was a significant change in performance from pre-test to post-test [$t(27) = -4.283$, $p = 0.010$], demonstrated as increased percent of correct trials at post-test (M = 81.38, SD = 11.75) compared to pre-

test (M = 68.14, SD = 19.86). In the prosaccade practice group, however, the change in percent correct from pre-test (M = 72.09, SD = 20.16) to post-test (M = 76.18, SD = 21.37) was not significant (p = 0.2). For percent correct of ODR trials, there was no significant effect of practice group, and there were no other interactions. See Figure 4.11.

Latency

Analysis of reaction time of correct ODR trials revealed a significant effect of time [$F(1,54) = 14.053$, $p < 0.001$], demonstrated as faster reaction times at post-test (M = 302.8ms, SE = 7.46) compared to pre-test (M = 339.7ms, SE = 10.41). There was also a marginally significant effect of diagnosis [$F(1,54) = 3.352$, $p = 0.066$], demonstrated as faster reaction times for the normal group (M = 306.9ms, SE = 10.93) compared to the schizophrenia group (M = 335.4ms, SE = 10.53). For reaction time of ODR trials, there was no significant effect of practice group, and there were no interactions. See Figure 4.12.

Gain

Analysis of gain of correct ODR trials revealed no significant effects of time, diagnosis or practice group, and there was no were no interactions. See Figure 4.13.

Practice Session Data

The eyetrack data collected during practice session (prosaccade-fixation and antisaccade-fixation) were analyzed using a 2 x 8 ANOVA (diagnosis x timepoint) with diagnosis being a between-subjects factors and timepoint entered as a within-subjects factor.

Prosaccade Percent Correct

Analysis of percent correct of prosaccades revealed no effect of time (p=0.868), diagnosis (p=0.250), nor a time by diagnosis interaction (p=0.738). See Figure 4.14.

Prosaccade Latency

Analysis of reaction time of prosaccades revealed a marginally significant effect of diagnosis [$F(1,26) = 2.981$, $p = 0.096$]. Although there was no main effect of time (p=0.195), both the normal and schizophrenia prosaccade practice groups showed a trend for decreasing latency of correct responses over time. Post-hoc independent samples t-tests were used to further identify diagnosis group-related influences on prosaccade performance. Analyses revealed a group difference demonstrated as faster reaction times for the normal group (M = 141.4ms, SE = 12.85) relative to the schizophrenia group (M = 178.8ms, SE = 12.85). While the normal group did show a significant effect of time [$F(7,91) = 13.745$, $p < 0.001$], no similar effect was found in the schizophrenia group ($p = 0.734$). For the normal group, paired sample t-tests revealed a significant decrease in latency from session 1 (M = 152.7ms, SD = 25.9) to session 4 (M = 141.8ms, SD = 21.4) [$t(14) = 3.008$, $p = 0.009$], as well as a significant decrease in latency from session 4 to session 8 (M = 132.5ms, SD = 16.4) [$t(14) = 4.173$, $p = 0.001$]. For the schizophrenia group, however, paired sample t-tests revealed no significant decreases in latency from session 1 (M = 184.5ms, SD = 104.4) to session 4 (M = 174.3ms, SD = 84.6) ($p = 0.678$), or from session 4 to session 8 (M = 165.6ms, SD = 53.8) ($p = 0.450$). For reaction time of prosaccades, there was no time by diagnosis interaction (p=0.777). See Figures 4.15-16.

Prosaccade Accuracy

Analysis of accuracy of prosaccades of 10 degree eccentricity revealed a marginally significant effect of diagnosis [$F(1,26) = 3.578$, $p = 0.070$]. Post-hoc independent samples t-tests were used to further identify diagnosis group-related influences. Analyses revealed a group difference demonstrated as a higher eccentricity of prosaccades for the normal group ($M = 12.51$ degrees, $SE = 0.252$) relative to the schizophrenia group ($M = 11.82$, $SE = 0.252$). There was no significant effect of time ($p=0.953$) or a time by diagnosis interaction ($p=0.949$). See Figure 4.17.

Analysis of accuracy of prosaccades of 5 degree eccentricity revealed no effect of time ($p=0.893$), diagnosis ($p=0.234$), nor a time by diagnosis interaction ($p=0.495$). See Figure 4.18.

Antisaccade Percent Correct

Analysis of percent correct of antisaccades revealed a marginally significant effect of diagnosis [$F(1,23) = 3.784$, $p = 0.064$]. Post-hoc independent samples t-tests were used to further identify diagnosis group-related influences on antisaccade performance. Analyses revealed a group difference demonstrated as a higher percent correct of antisaccades for the normal group ($M = 77.22$, $SE = 5.558$) relative to the schizophrenia group ($M = 61.61$, $SE = 5.785$). There was no significant effect of time ($p=0.922$) or a time by diagnosis interaction ($p=0.284$). See Figures 4.19-20.

Antisaccade Latency

Analysis of reaction time of antisaccades revealed a significant effect of time [$F(7,161) = 3.182$, $p = 0.004$] and a significant effect of diagnosis [$F(1,23) = 6.607$, $p =$

0.017]. Post-hoc independent samples t-tests were used to further identify diagnosis group-related influences on antisaccade performance. Analyses revealed a group difference demonstrated as faster reaction times for the normal group (M = 199.6ms, SE = 13.8) relative to the schizophrenia group (M = 250.9ms, SE = 14.3). Post-hoc independent samples t-tests were also used to further identify time-related influences on antisaccade performance. Analyses revealed a significant time difference between session 1 and session 2 [t(25) = 2.893, p = 0.008] demonstrated as faster reaction times for session 2 (M = 227.5ms, SD = 45.9) relative to session 1 (M = 242.8ms, SD = 57.5). There was also a significant time difference between session 1 and session 8 [t(27) = 2.893, p = 0.007] demonstrated as faster reaction times for session 8 (M = 222.8ms, SD = 67.5) relative to session 1. There were no significant differences in reaction time between any of the other sessions (session 2 vs session 3, session 3 vs session 4, session 4 vs session 5, session 5 vs session 6, session 6 vs session 7, session 7 vs session 8). Also, there was no time by diagnosis interaction (p=0.164). See Figures 4.21-22.

Antisaccade Accuracy

Analysis of accuracy of antisaccades of 10 degree eccentricity revealed no effect of time (p=0.135), diagnosis (p=0.790), nor a time by diagnosis interaction (p=0.471). See Figure 4.23.

Analysis of accuracy of antisaccades of 5 degree eccentricity revealed a significant effect of time [F(7,161) = 4.513, p = 0.026]. Post-hoc independent samples t-tests were used to further identify time-related influences on antisaccade eccentricity. Analyses revealed a significant time difference between session 2 and session 3 [t(25) = 2.797, p = 0.010] demonstrated as higher eccentricity for session 2 (M = 7.28 degrees,

SD = 3.48) relative to session 3 (M = 6.70 degrees, SD = 3.18). There was also a marginally significant time difference between session 1 and session 8 [t(27) = 1.793, p = 0.093] demonstrated as higher eccentricity for session 1 (M = 7.55 degrees, SD = 3.23) relative to session 8 (M = 6.64 degrees, SD = 2.74). There were no significant differences in reaction time between any of the other sessions (session 1 vs session 2, session 3 vs session 4, session 4 vs session 5, session 5 vs session 6, session 6 vs session 7, session 7 vs session 8). Also, there was no effect of diagnosis (p=0.331) and no time by diagnosis interaction (p=0.230). See Figure 4.24.

Antisaccade Speed-Accuracy Tradeoff

Analysis of speed accuracy tradeoff for antisaccades (i.e., percent correct of antisaccades versus reaction time of correct antisaccades) revealed significant correlations for data collapsed across all eight timepoints for both the normal antisaccade practice group (r = 0.206, p = 0.036) and the schizophrenia antisaccade practice group (r = 0.400, p < 0.001). Post-hoc analyses, however, revealed no significant correlations at any single session for the normal antisaccade practice group [session 1 (r = 0.435, p = 0.138), session 2 (r = -0.095, p = 0.758), session 3 (r = 0.172, p = 0.573), session 4 (r = 0.217, p = 0.476), session 5 (r = 0.241, p = 0.428), session 6 (r = 0.273, p = 0.367), session 7 (r = 0.188, p = 0.539), session 8 (r = 0.203, p = 0.506)]. For the schizophrenia antisaccade practice group, significant correlations were present during various sessions [session 1 (r = 0.319, p = 0.247), **session 2** (r = 0.591, p = 0.033), session 3 (r = 0.394, p = 0.147), session 4 (r = 0.460, p = 0.085), session 5 (r = 0.319, p = 0.247), **session 6** (r = 0.609, p = 0.016), session 7 (r = 0.518, p = 0.580), session 8 (r = 0.254, p = 0.361)]. See Figures 4.25-26.

Scanner Session Eye Movement Data

The eyetrack data collected during scanning sessions for the each of the three behavioral paradigms (prosaccade-fixation, antisaccade-fixtion, and antisaccade-prosaccade) were analyzed using a 2 x 2 x 3 ANOVA (diagnosis x practice group x timepoint) with all factors except timepoint being between-subjects factors (timepoint was entered as a within-subjects factor).

Prosaccade Percent Correct

Analysis of percent correct of all prosaccades (combined from the prosaccade-fixation and antisaccade-prosaccade paradigms) revealed no significant effects of diagnosis, practice group or time, and there were no interaction effects. See Figure 4.27.

Analysis of percent correct of prosaccades from the prosaccade-fixation paradigm revealed a significant diagnosis by practice group by time interaction [$F(2,96) = 3.772$, $p = 0.026$]. Post-hoc independent samples t-tests were used to further identify practice group-related influences on prosaccade performance. Among all subjects, there were no significant differences between the antisaccade- and prosaccade-practice groups at any of the timepoints. Further analyses confirmed a practice group difference in the normal group at pre-test at the trend level [$t(26) = -1.93$, $p = 0.65$], demonstrated as slightly better performance for the antisaccade practice group ($M = 99.36$, $SD = 1.68$) relative to the prosaccade practice group ($M = 96.86$, $SD = 4.39$). There were no other practice group differences over time in the normal group. For the schizophrenia group, additional analyses revealed practice group influences over prosaccade performance at post-test [$t(26) = 3.324$, $p = 0.003$]. This effect was demonstrated by a greater percent of correct prosaccades for the prosaccade group ($M = 98.92$, $SD = 1.94$) relative to the antisaccade

group (M = 93.42, SD = 6.09). There were no other practice group differences over time in the schizophrenia group. Paired samples tests were used to further identify time-related influences on prosaccade performance. Among all subjects, prosaccade performance worsened from pre-test to post-test [t(54) = 2.323, p = 0.024]. There were no significant differences in prosaccade performance from pre-test to mid-test (p=0.35) or from mid-test to post-test (p = 0.60). This effect was apparent among the normal group, demonstrated by a marginal decline in performance from pre-test to post-test [t(27) = 1.734, p = 0.94]. Among the normal group, there were not significant changes in prosaccade performance from pre-test to mid-test (p = 0.87), nor from mid-test to post-test (p = 0.23). In the schizophrenia group, there were no significant changes in prosaccade performance over time (pre-test to mid-test, p = 0.36; mid-test to post-test, p = 0.83), however, from pre-test to post-test, there was a sub-trend-level decline in prosaccade performance [t(26)=1.537, p = 0.136]. See Figure 4.28.

Analysis of percent correct of prosaccades from the antisaccade-prosaccade paradigm revealed a marginally significant main effect of practice group [F(1,45) = 3.686, p = 0.061], shown as greater percentage correct for the prosaccade practice group (M = 96.770, SE = 0.921) compared to the antisaccade practice group (M = 94.295, SE = 0.903). For percent correct of prosaccades from the antisaccade-prosaccade paradigm, there were no main effects of diagnosis or time, and there were not interaction effects. See Figure 4.29.

Prosaccade Latency

Analysis of reaction time of prosaccades (combined from the prosaccade-fixation and antisaccade-prosaccade paradigms) revealed a marginally significant main effect of

practice group [F(1,43) = 3.194, p = 0.081], shown as greater latency for the prosaccade practice group (M = 186.9ms, SE = 7.45) compared to the antisaccade practice group (M = 167.8ms, SE = 7.617). Paired sample t-tests, however, revealed a significant decrease in reaction time for the normal prosaccade practice group between pre-test (M = 186.4ms, SD = 25.9) and mid-test (M = 168.4ms, SD = 22.7) [t(12) = 3.2993, p = 0.006], and from pre-test to post-test (M = 165.1ms, SD = 24.0) [t(12) = 4.023, p = 0.002]. The difference between mid-test and post-test, however, was not significant (p = 0.392). For the schizophrenia prosaccade practice group, paired sample tests revealed no significant changes in reaction time between any of the time points. For reaction time of prosaccades combined from the prosaccade-fixation and antisaccade-prosaccade paradigms, there were no main effects of diagnosis or time, and there were not interaction effects. See Figure 4.30.

Analysis of reaction time of prosaccades from the prosaccade-fixation paradigm revealed a marginally significant main effect of practice group [F(1,42) = 3.159, p = 0.083], shown as greater latency for the prosaccade practice group (M = 183.9ms, SE = 7.56) compared to the antisaccade practice group (M = 164.5ms, SE = 7.929). Paired sample t-tests, however, revealed a significant decrease in reaction time for the normal prosaccade practice group between pre-test (M = 185.0ms, SD = 25.0) and mid-test (M = 168.4ms, SD = 21.8) [t(12) = 3.296, p = 0.006], and from pre-test to post-test (M = 162.2ms, SD = 25.3) [t(12) = 5.041, p < 0.001]. The difference between mid-test and post-test, however, was not significant (p = 0.206). For the schizophrenia prosaccade practice group, paired sample tests revealed no significant changes in reaction time between any of the time points. For reaction time of prosaccades from the prosaccade-

fixation paradigm, there were no main effects of diagnosis or time, and there were no interaction effects. For the normal antisaccade practice group, there was not a significant main effect of time [$F(2,18) = 0.239$, $p = 0.790$], and there were no significant changes in prosaccade latency from pre-test to mid-test ($p = 0.577$), from mid-test to post-test ($p = 0.606$), or from pre-test to post-test ($p = 0.703$). For the schizophrenia antisaccade practice group, there was not a significant effect of time [$F(2,22) = 0.046$, $p = 0.955$], and there were no significant changes in prosaccade latency from pre-test to mid-test ($p = 0.952$), from mid-test to post-test ($p = 0.689$), or from pre-test to post-test ($p = 0.989$). See Figure 4.31.

Analysis of reaction time of prosaccades from the antisaccade-prosaccade paradigm revealed a marginally significant main effect of diagnosis group [$F(1,40) = 3.022$, $p = 0.090$], shown as greater latency for the schizophrenia group ($M = 190.2$ms, $SE = 8.09$) compared to the normal group ($M = 169.8$ms, $SE = 8.475$). Paired sample t-tests, however, revealed a significant decrease in reaction time for the normal prosaccade practice group between pre-test ($M = 180.4$ms, $SD = 24.7$) and mid-test ($M = 166.3$ms, $SD = 26.0$) [$t(10) = 2.864$, $p = 0.017$], and from pre-test to post-test ($M = 167.7$ms, $SD = 23.8$) [$t(12) = 2.860$, $p = 0.014$]. The difference between mid-test and post-test, however, was not significant ($p = 0.806$). For the schizophrenia prosaccade practice group, paired sample t-tests revealed no significant changes in reaction time between any of the time points. For reaction time of prosaccades from the antisaccade-prosaccade paradigm, there were no main effects of diagnosis or time, and there were no interaction effects. For the normal antisaccade practice group, there was not a significant main effect of time [$F(2,20) = 0.006$, $p = 0.994$], and there were no significant changes in prosaccade latency

from pre-test to mid-test (p = 0.839), from mid-test to post-test (p = 0.909), or from pre-test to post-test (p = 0.996). For the schizophrenia antisaccade practice group, there was not a significant effect of time [F(2,22) = 0.076, p = 0.927], and there were no significant changes in prosaccade latency from pre-test to mid-test (p = 0.741), from mid-test to post-test (p = 0.542), or from pre-test to post-test (p = 0.818). See Figure 4.32.

Prosaccade Accuracy

Analysis of amplitude of prosaccades of 10 degree eccentricity (combined from the prosaccade-fixation and antisaccade-prosaccade paradigms) revealed a significant effect of diagnosis [F(1,43) = 6.604, p = 0.014], demonstrated as higher amplitude in the normal group (M = 10.34 degrees, SE = 0.377) compared to the schizophrenia group (M = 8.98 degrees, SE = 0.369). There were no effects of time or practice group, and there were no interaction effects. See Figure 4.33.

Analysis of amplitude of prosaccades of 5 degree eccentricity (combined from the prosaccade-fixation and antisaccade-prosaccade paradigms) revealed a significant effect of diagnosis [F(1,43) = 4.987, p = 0.031], demonstrated as higher amplitude in the normal group (M = 5.67 degrees, SE = 0.214) compared to the schizophrenia group (M = 5.004 degrees, SE = 0.209). There were no effects of time or practice group, and there were no interaction effects. See Figure 4.34.

Antisaccade Percent Correct

Analysis of percent correct of antisaccades (combined from the antisaccade-fixation and antisaccade-prosaccade paradigms) revealed a significant diagnosis by time interaction [F(2,96) = 3.772, p = 0.026]. Post-hoc independent samples t-tests were used

to further identify diagnosis group-related influences on antisaccade performance. Further analyses confirmed a significant difference at pre-test [$t(55) = 2.775$, $p = 0.008$], demonstrated as better performance for the normal group ($M = 77.47\%$, $SD = 1.29$) relative to the schizophrenia group ($M = 61.67\%$, $SD = 2.79$), and a significant difference at mid-test [$t(54) = 2.023$, $p = 0.048$], demonstrated again as better performance for the normal group ($M = 77.92\%$, $SD = 1.69$) relative to the schizophrenia group ($M = 65.56\%$, $SD = 2.75$). There was no significant diagnosis group difference at post-test. Paired samples tests were used to further identify time-related influences on antisaccade performance. Among all subjects, there were no significant differences in antisaccade performance from pre-test to mid-test ($p=0.275$), from mid-test to post-test ($p = 0.276$), or from pre-test to post-test ($p = 0.641$). In the normal group, there was a marginally significant change in performance from mid-test to post-test [$t(26) = 1.984$, $p = 0.058$], demonstrated by a greater percentage of correct responses at mid-test ($M = 78.10$, $SD = 1.72$) compared to post-test ($M = 74.59$, $SD = 1.71$). Among the normal group, however, there were not significant changes in antisaccade performance from pre-test to mid-test ($p = 0.953$), nor from pre-test to post-test ($p = 0.100$). In the schizophrenia group, there was a significant change in performance from pre-test to post-test [$t(26) = -2.526$, $p = 0.018$], demonstrated by a greater percentage of correct responses at post-test ($M = 67.95$, $SD = 2.68$) compared to pre-test ($M = 61.69$, $SD = 2.80$). Among the schizophrenia group, however, there were not significant changes in antisaccade performance from pre-test to mid-test ($p = 0.136$), nor from mid-test to post-test ($p = 0.278$). In addition to the significant diagnosis by time interaction, preliminary analyses also revealed a marginally significant main effect of diagnosis [$F(1,48) = 3.135$, $p = 0.083$], demonstrated as greater

percentage correct scores for the normal group (M = 76.393, SE = 3.959) compared to the schizophrenia group (M = 66.494, SE = 3.948). There was also a marginally significant diagnosis by practice interaction [F(1,48) = 2.986, p = 0.090], and a significant main effect of practice group [F(1,48) = 4.781, p = 0.035], demonstrated as greater percentage correct scores for the prosaccade practice group (M = 77.516, SE = 3.877) compared to the antisaccade practice group (M = 65.371, SE = 4.029). Paired samples post-hoc tests revealed that for the normal antisaccade practice group, there was no main effect of time (p = 0.903), and there were no significant differences between the three timepoints. Similarly for the schizophrenia antisaccade practice group, there was no main effect of time (p = 0.248), and there were no significant differences between the three timepoints. For the normal prosaccade practice group, there was a significant main effect of time [F(2,26) = 7.054, p = 0.004], demonstrated as significant decreases in performance from pre-test (M = 81.12, SD = 11.6) to post-test (M = 72.07, SD = 17.0) [t(14) = 3.292, p = 0.005], and from mid-test (M = 79.33, SD = 14.0) to post-test [t(13) = 3.361, p = 0.005], but not from pre-test to mid-test (p = 0.438). or the schizophrenia prosaccade practice group, there was not a significant main effect of time [F(2,24) = 1.427, p = 0.260]. The trend for this groups to appears to be increasing performance over time, however, the only significant change was from pre-test (M = 70.97, SD = 24.6) to post-test (M = 76.98, SD = 24.0) [t(13) = -2.506, p = 0.026]. The increase in performance was not significant from pre-test to mid-test (p = 0.587) or from mid-test to post-test (p = 0.277). See Figure 4.35.

Analysis of percent correct of antisaccades from the antisaccade-fixation paradigm revealed a marginally significant main effect of practice group [F(1,45) =

3.447, p = 0.070], shown as greater percentage correct for the prosaccade practice group (M = 77.95, SE = 3.556) compared to the antisaccade practice group (M = 68.052, SE = 3.965). Paired samples post-hoc tests revealed that for the normal antisaccade practice group, there was no main effect of time (p = 0.617), and there were no significant differences between the three timepoints. Similarly for the schizophrenia antisaccade practice group, there was no main effect of time (p = 0.431), and there were no significant differences between the three timepoints. For percent correct of antisaccades from the antisaccade-fixation paradigm, there were no main effects of diagnosis or time, and there were not interaction effects. For the normal prosaccade practice group, there was a significant main effect of time [F(2,26) = 4.750, p = 0.017], demonstrated as a significant increase in performance from pre-test (M = 77.84, SD = 17.3) to mid-test (M = 83.65, SD = 11.5) [t(13) = -2484, p = 0.027] and significant decrease in performance from mid-test to post-test (M = 72.98, SD = 18.8) [t(13) = 2.882, p = 0.013], but no significant change pre-test to post-test (p = 0.438). For the schizophrenia prosaccade practice group, there was not a significant main effect of time [F(2,24) = 2.004, p = 0.157]. The trend for this group to appears to be increasing performance over time, however, the only significant change was from pre-test (M = 75.34, SD = 20.8) to post-test (M = 81.41, SD = 19.6) [t(12) = -2.776, p = 0.017]. The increase in performance was not significant from pre-test to mid-test (p = 0.764) or from mid-test to post-test (p = 0.357). See Figure 4.36.

Analysis of percent correct of antisaccades from the antisaccade-prosaccade paradigm revealed a significant diagnosis by time interaction [F(2,90) = 6.690, p = 0.002]. Post-hoc independent samples t-tests were used to further identify diagnosis

group-related influences on antisaccade performance. Further analyses confirmed a significant difference at pre-test [t(55) = 3.151, p = 0.003], demonstrated as better performance for the normal group (M = 79.92.47, SD = 1.34) relative to the schizophrenia group (M = 60.66, SD = 2.95), and a marginally significant difference at mid-test [t(54) = 1.913, p = 0.061], demonstrated again as better performance for the normal group (M = 76.01, SD = 1.80) relative to the schizophrenia group (M = 63.58, SD = 2.80). There was no significant diagnosis group difference at post-test. Paired samples tests were used to further identify time-related influences on antisaccade performance. Among all subjects, there were no significant differences in antisaccade performance from pre-test to mid-test (p=0.907), from mid-test to post-test (p = 0.986), or from pre-test to post-test (p = 0.755). In the normal group, there was a significant change in performance from pre-test to post-test [t(26) = 3.625, p = 0.001], demonstrated by a greater percentage of correct responses at pre-test (M = 80.60, SD = 1.31) compared to post-test (M = 72.94, SD = 1.67). Among the normal group, however, there were not significant changes in antisaccade performance from pre-test to mid-test (p = 0.122), nor from mid-test to post-test (p = 0.170). In the schizophrenia group, there was a significant change in performance from pre-test to post-test [t(26) = -2.227, p = 0.035], demonstrated by a greater percentage of correct responses at post-test (M = 67.07, SD = 2.70) compared to pre-test (M = 60.69, SD = 3.00). Among the schizophrenia group, however, there were not significant changes in antisaccade performance from pre-test to mid-test (p = 0.130), nor from mid-test to post-test (p = 0.310). Paired samples post-hoc tests revealed that for the normal antisaccade practice group, there was no main effect of time (p = 0.873), and there were no significant differences between the three timepoints.

Similarly for the schizophrenia antisaccade practice group, there was no main effect of time ($p = 0.157$), and there were no significant differences between the three timepoints. For the normal prosaccade practice group, there was a significant main effect of time [$F(2,22) = 8.368$, $p = 0.002$], demonstrated as significant decreases in performance from pre-test ($M = 83.69$, $SD = 9.6$) to post-test ($M = 70.94$, $SD = 18.0$) [$t(14) = 4.846$, $p < 0.001$], and from mid-test ($M = 75.86$, $SD = 17.6$) to post-test [$t(11) = 2.208$, $p = 0.049$], and a marginally significant decrease from pre-test to mid-test ($p = 0.064$). For the schizophrenia prosaccade practice group, there was not a significant effect of time [$F(2,22) = 0.458$, $p = 0.639$]. The trend for this groups to appears to be increasing performance over time, however, there were no significant changes from pre-test to mid-test ($p = 0.637$), from mid-test to post-test ($p = 0.392$) or from pre-test to post-test ($p = 0.129$). See Figure 4.37.

Antisaccade Latency

Analysis of reaction time of antisaccades (combined from the antisaccade-fixation and antisaccade-prosaccade paradigms) revealed significant effects for time [$F(2,86) = 4.191$, $p = 0.018$], diagnosis [$F(1,43) = 5.178$, $p = 0.028$], time by diagnosis [$F(2,86) = 6.188$, $p = 0.003$], and time by practice group [$F(2,86) = 3.775$, $p = 0.027$]. Post-hoc independent samples t-tests were used to further identify diagnosis and practice group-related influences on antisaccade performance. Further analyses confirmed a significant difference at mid-test [$t(54) = -3.553$, $p = 0.001$], demonstrated as faster latency in the normal group ($M = 241.6$, $SD = 4.48$) relative to the schizophrenia group ($M = 295.2$, $SD = 6.60$), and a significant difference at post-test [$t(52) = -3.909$, $p < 0.001$], demonstrated again as faster latency in the normal group ($M = 240.0$, $SD = 3.69$) relative to the

schizophrenia group (M = 296.0, SD = 6.38). There was no significant diagnosis group difference at pre-test. Independent samples t-tests revealed no significant differences between practice groups at either pre-test, mid-test, or post-test. Paired samples tests were used to further identify time-related influences on antisaccade performance. Among all subjects, there was a significant difference in reaction time between pre-test to mid-test [$t(50) = 2.817$, $p = 0.007$] demonstrated as faster reaction times at mid-test (M = 269.0ms, SD = 6.32) compared to pre-test (M = 287.7ms, SD = 5.78), and a significant difference in reaction time between pre-test and post-test [$t(48) = 2.283$, $p = 0.027$], demonstrated as faster reaction times at post-test (M = 270.3ms, SD = 6.05) compared to pre-test. The difference between mid-test and post-test, however, was not significant ($p = 0.720$). In the normal group, there was a significant change in performance from pre-test to mid-test [$t(25) = 4.029$, $p < 0.001$], demonstrated by a faster reaction times at mid-test (M = 242.2ms, SD = 4.62) compared to pre-test (M = 276.1ms, SD = 6.00), and a significant change in performance from pre-test to post-test [$t(23) = 3.609$, $p = 0.001$], demonstrated by a faster reaction times at post-test (M = 240.8ms, SD = 3.83) compared to pre-test. Among the normal group, however, there were not significant changes in reaction time from mid-test to post-test ($p = 0.261$). In the schizophrenia group, there were no significant changes in reaction time from pre-test to mid-test ($p = 0.766$), from mid-test to post-test ($p = 0..902$), or from pre-test to post-test ($p=0.824$). For the prosaccade practice group, there was a significant change in performance from pre-test to mid-test [$t(24) = 2.089$, $p = 0.047$], demonstrated by faster reaction times at mid-test (M = 278.6ms, SD = 6.53) compared to pre-test (M = 300.8ms, SD = 6.48), and a significant change in performance from pre-test to post-test [$t(25) = 3.314$, $p = 0.003$], demonstrated

by faster reaction times at post-test (M = 271.0ms, SD = 5.63) compared to pre-test. Among the prosaccade practicers, however, there were not significant changes in reaction time from mid-test to post-test (p = 0.112). In the antisaccade practice group, however, there were no significant changes in reaction time from pre-test to mid-test (p = 0.074), from mid-test to post-test (p = 0.140), or from pre-test to mid-test (p=0.853). See Figure 4.38.

Analysis of reaction time of antisaccades from the antisaccade-fixation paradigm revealed significant effects for diagnosis [F(1,41) = 11.49, p = 0.002], time by diagnosis [F(2,82) = 3.417, p = 0.038], and time by practice group [F(2,82) = 3.141, p = 0.048]. Post-hoc independent samples t-tests were used to further identify diagnosis and practice group-related influences on antisaccade performance. Further analyses confirmed a significant difference at mid-test [t(51) = -3.352, p = 0.001], demonstrated as faster latency in the normal group (M = 238.9ms, SD = 4.71) relative to the schizophrenia group (M = 291.3, SD = 5.94), and a significant difference at post-test [t(50) = -4.149, p < 0.001], demonstrated again as faster latency in the normal group (M = 237.3ms, SD = 3.90) relative to the schizophrenia group (M = 300.5ms, SD = 6.62). There was no significant diagnosis group difference at pre-test (p = 0.228). Independent samples t-tests revealed no significant differences between practice groups at either pre-test, mid-test, or post-test. Paired samples tests were used to further identify time-related influences on antisaccade performance. Among all subjects, there was a significant difference in reaction time between pre-test to mid-test [t(47) = 2.463, p = 0.018] demonstrated as faster reaction times at mid-test (M = 264.5ms, SD = 5.90) compared to pre-test (M = 287.1ms, SD = 5.61). The differences between mid-test and post-test (p = 0.717) as well

as pre-test and post-test ($p = 0.153$), however, were not significant. In the normal group, there was a significant change in performance from pre-test to mid-test [$t(23) = 2.823$, $p = 0.010$], demonstrated by a faster reaction times at mid-test ($M = 239.6$ms, $SD = 4.90$) compared to pre-test ($M = 267.4$ms, $SD = 5.48$), and a significant change in performance from pre-test to post-test [$t(22) = 3.160$, $p = 0.005$], demonstrated by a faster reaction times at post-test ($M = 236.2$ms, $SD = 3.99$) compared to pre-test. Among the normal group, however, there were not significant changes in reaction time from mid-test to post-test ($p = 0.241$). In the schizophrenia group, there were no significant changes in reaction time from pre-test to mid-test ($p = 0.541$), from mid-test to post-test ($p = 0.878$), or from pre-test to post-test ($p=0.533$). For the prosaccade practice group, there was a significant change in performance from pre-test to mid-test [$t(24) = 2.850$, $p = 0.009$], demonstrated by faster reaction times at mid-test ($M = 275.9$ms, $SD = 5.91$) compared to pre-test ($M = 296.5$ms, $SD = 5.53$), and a significant change in performance from pre-test to post-test [$t(23) = 2.909$, $p = 0.008$], demonstrated by a faster reaction times at post-test ($M = 271.2$ms, $SD = 6.42$) compared to pre-test. Among the prosaccade practicers, however, there were not significant changes in reaction time from mid-test to post-test ($p = 0.219$). In the antisaccade practice group, however, there were no significant changes in reaction time from pre-test to mid-test ($p = 0.304$), from mid-test to post-test ($p = 0.326$), or from pre-test to post-test ($p=0.647$). For the normal prosaccade practice group, there was a significant main effect of time [$F(2,22) = 11.225$, $p < 0.001$], demonstrated as a significant decrease in latency from pre-test ($M = 283.9$ms, $SD = 55.5$) to mid-test ($M = 251.0$ms, $SD = 57.0$) [$t(12) = 3.248$, $p = 0.007$] and from pre-test to post-test ($M = 244.6$ms, $SD = 43.1$) [$t(11) = 4.113$, $p = 0.002$], but no significant change from mid-test

to post-test ($p = 0.212$). For the schizophrenia prosaccade practice group, there was not a significant effect of time [$F(2,22) = 0.401$, $p = 0.674$]. The trend for this groups appears to be generally steady latency over time, and there were no significant changes from pre-test to mid-test ($p = 0.449$), from mid-test to post-test ($p = 0.487$) or from pre-test to post-test ($p = 0.447$). See Figure 4.39.

Analysis of reaction time of antisaccades from the antisaccade-prosaccade paradigm revealed a significant effect of diagnosis [$F(1,40) = 10.640$, $p = 0.002$], demonstrated as faster reaction times in the normal group ($M = 248.1$ms, $SE = 11.509$) compared to the schizophrenia group ($M = 300.0$ms, $SE = 10.995$). The 3-way ANOVA also revealed a marginally significant time effect [$F(2,80) = 2.979$, $p = 0.057$], time by diagnosis interaction [$F(2,80) = 2.456$, $p = 0.092$], and time by practice group interaction [$F(2,80) = 2.438$, $p = 0.094$]. For the normal prosaccade practice group, there was a significant main effect of time [$F(2,18) = 9.168$, $p = 0.002$], demonstrated as a significant decrease in latency from pre-test ($M = 267.1$ms, $SD = 57.7$) to mid-test ($M = 241.9$ms, $SD = 47.2$) [$t(10) = 4.849$, $p = 0.001$], a marginally significant decrease from pre-test to post-test ($M = 252.1$ms, $SD = 42.5$) [$t(12) = 2.139$, $p = 0.054$], but no significant change from mid-test to post-test ($p = 0.636$). For the schizophrenia prosaccade practice group, there was not a significant effect of time [$F(2,20) = 1.580$, $p = 0.231$]. There was, however, a significant decrease in antisaccade latency between pre-test ($M = 313.8$ms, $SD = 72.0$) and post-test ($M = 285.0$ms, $SD = 56.3$) [$t(12) = 2.489$, $p = 0.028$], but no significant change from pre-test to mid-test ($p = 0.9499$) or from mid-test to post-test ($p = 0.188$). See Figure 4.40.

Antisaccade Accuracy

Analysis of amplitude of antisaccades of 10 degree eccentricity (combined from the antisaccade-fixation and antisaccade-prosaccade paradigms) revealed a significant effect of diagnosis [$F(1,43) = 5.140$, $p = 0.028$], demonstrated as higher amplitude in the normal group ($M = 7.86$ degrees, $SE = 0.446$) compared to the schizophrenia group ($M = 6.456$ degrees, $SE = 0.436$). There were no effects of time or practice group, and there were no interaction effects. See Figure 4.41.

Analysis of amplitude of antisaccades of 5 degree eccentricity (combined from the antisaccade-fixation and antisaccade-prosaccade paradigms) revealed a significant effect of time [$F(2,86) = 4.081$, $p = 0.020$]. Post-hoc independent t-tests revealed a significant difference between pre-test and mid-test [$t(50) = 3.507$, $p = 0.001$], demonstrated as a decrease in amplitude at mid-test ($M = 5.28$ degrees, $SD = 2.02$) compared to pre-test ($M = 6.14$ degress, $SD = 2.40$). There were no significant changes from mid-test to post-test ($p = 0.283$) or from pre-test to post-test ($p = 0.283$). There were no effects of diagnosis or practice group, and there were no interaction effects. See Figure 4.42.

Antisaccade Speed-Accuracy Tradeoff

Pre-Test

Analyses between percent correct and reaction time of antisaccades (from the antisaccade-fixation paradigm) at pre-test revealed no significant correlations for all subjects, the normal group, the schizophrenia group, the prosaccade practice group, or the antisaccade practice group. Further analyses revealed a slightly positive correlation for the normal antisaccade practice group ($r = 0.094$, $p = 0.784$), a slightly negative

correlation for the normal prosaccade practice group (r = -0.126, p = 0.669), a strong positive correlation for the schizophrenia antisaccade practice group (r = 0.743, p = 0.004), and a strong positive correlation for the schizophrenia prosaccade practice group (r = 0.832, p < 0.001).

Mid-Test

Analyses between percent correct and reaction time of antisaccades (from the antisaccade-fixation paradigm) at mid-test revealed a significant positive correlation for the schizophrenia group (r = +0.598, p = 0.001). There were no significant correlations, however, for all subjects, the normal group, the prosaccade practice group, or the antisaccade practice group. Further analyses revealed a slightly positive correlation for the normal antisaccade practice group (r = 0.129, p = 0.689), a slightly negative correlation for the normal prosaccade practice group (r = -0.120, p = 0.683), a strong positive correlation for the schizophrenia antisaccade practice group (r = 0.602, p = 0.029), and a moderate positive correlation for the schizophrenia prosaccade practice group (r = 0.365, p = 0.199).

Post-test

Analyses between percent correct and reaction time of antisaccades (from the antisaccade-fixation paradigm) at post-test revealed no significant correlations for all subjects, the normal group, the schizophrenia group, the prosaccade practice group, or the antisaccade practice group. Further analyses revealed a slightly positive correlation for the normal antisaccade practice group (r = 0.295, p = 0.392), a moderate negative

correlation for the normal prosaccade practice group (r = -0.452, p = 0.121), a weak negative correlation for the schizophrenia antisaccade practice group (r = -0.011, p = 0971), and a slightly negative correlation for the schizophrenia prosaccade practice group (r = -0.204, p = 0.484). See Figures 4.43-47 for correlation graphs for pre-, mid-, and post-test.

FMRI Data

Data for the antisaccade/fixation paradigm were run in an independent components analysis. The three averages (one for each timepoint) were concatenated in space, and Probabilistic ICA (PICA) was performed using MELODIC (Beckmann & Smith, 2004). PICA revealed 42 separate components, the first 8 of which were task-related. Components 1, 2, and 4 were most associated with the pre-test session, components 3 and 5 were most associated with the mid-test session, and components 6, 7, and 8 were most associated with the post-test session. See Figures 4.48-50.

Preliminary Analysis

Results from the whole-brain analyses of the antisaccade-fixation run (collapsed over all three timepoints) are shown in Figure 4.51. For this analysis, 24 artifact and/or motion regressors were used in the GLM. The following regions showed significant changes in BOLD signal activation associated with task performance: supplementary eye fields (SEF), bilateral lateral frontal eye fields (Lat FEF), bilateral medial frontal eye fields (Med FEF), bilateral PFC, bilateral inferior frontal cortex (IFC), bilateral precuneus, bilateral cuneus, bilateral inferior parietal lobule (IPL), bilateral middle

occipital gyrus (MOG), bilateral striatum, bilateral thalamus, bilateral inferior frontal gyrus BA 44 (IFG-44), bilateral insula, and bilateral cerebellum. Results from the whole-brain analyses of the antisaccade-fixation run at pre-test, mid-test, and post-test are shown in Figures 4.52-54. For all images, a threshold/cluster method derived from Monte Carlo simulations was applied to the t-map (Ward, 2000) to protect against false positives (See Analysis – FMRI Data). Based on these simulations, the family-wise alpha of 0.05 was preserved with an a priori voxelwise probability of 0.025 and three-dimensional clusters with a minimum volume of 1088 µl (17 or more voxels).

Between- and Within-Groups T-Tests

Imaging data for the antisaccade-fixation runs were entered into between-groups t-tests to determine differences in regional activity. After using Monte Carlo simulations to protect against false positives, three maps yielded significant differences. Collapsing across time, the normal group demonstrated significantly greater activity in a number of regions supporting antisaccade performance compared to the schizophrenia group (see Figure 4.55). These regions included most notably bilateral FEF, PFC, precuneus, IFC, IFG BA 44, MOG, striatum, and cerebellum. The schizophrenia group did not demonstrate greater activity than the normal group in any region. Collapsing across time, the prosaccade- and antisaccade-practice groups demonstrated significantly different activity in several regions (see Figure 4.56). The prosaccade-practice group demonstrated greater activity in right inferior parietal lobule, and the antisaccade-practice group demonstrated greater activity in right post-central gyrus at BA 2, left pre-central gyrus at BA 6, and at a cluster near the most superior regions of left post-central gyrus near BA 3. Within subjects analyses revealed significant differences between pre-test

and post-test (see Figure 4.57). All differences were demonstrated as increased signal at pre-test compared to post-test in the following regions: SEF, bilateral medial FEF, bilateral lateral FEF, bilateral PFC, bilateral precuneus, left IFG BA 44, left IPL, left insula, and right middle temporal gyrus. There were no significant differences in any regions between activity from pre-test to mid-test or from mid-test to post-test.

ROI Analysis

ROIs were determined based on BOLD activations from the whole-brain analyses of the antisaccade-fixation run (collapsed over all three timepoints) as shown in Figure 4.58. For each ROI, a sphere of radius 8 mm was positioned at the center of mass of each region, and mean percent signal changes for each run were calculated for each ROI for each individual. In total there were 27 separate regions (see Table 4.1 for a list of regions and their respective coordinates; see Figure 4.44 for the regions overlayed on the t-map). Note that posterior cingulate gyrus did not survive clustering and was not included in the ROI set.

The 26 bilateral ROIs (excluding SEF) were analyzed using a 2 x 2 x 2 x 3 ANOVA (diagnosis x practice group x laterality x timepoint) with all factors except time being between-subjects factors (timepoint was entered as a within-subjects factor). The 4-way ANOVA yielded a significant main effect of laterality for precuneus [$F(1,104) = 8.503$, $p = 0.043$], a marginally significant main of effect of laterality for insula [$F(1,104) = 3.190$, $p = 0.077$], and a marginally significant interaction effect of practice by laterality for IPL [$F(1, 104) = 3.231$, $p = 0.075$]. Thus, the left and right components of each of these regions were treated separately, and all other ROIs were averaged between their left and right components.

Analysis of SEF revealed a significant effect of time [$F(2, 104) = 4.247$, $p = 0.017$], demonstrated by a significant decrease in activity from pre-test ($M = 0.327$, $SE = 0.028$) to post-test ($M = 0.206$, $SE = 0.029$) (pairwise comparison: $p = 0.003$), and a marginally significant decrease in activity from pre-test to mid-test ($M = 0.245$, $SE = 0.036$) (pairwise comparison: $p = 0.070$). The pairwise comparison between activity from mid-test to post-test was not significant ($p = 0.373$). For SEF, there were no main effects of diagnosis or practice group, and there were no interaction effects. See Figure 4.59.

Analysis of bilateral lateral FEF revealed a marginally significant effect of time [$F(2, 104) = 2.893$, $p = 0.060$], demonstrated by a significant decrease in activity from pre-test ($M = 0.268$, $SE = 0.018$) to post-test ($M = 0.208$, $SE = 0.019$) (pairwise comparison: $p = 0.002$). The pairwise comparisons between activity from pre-test to mid-test ($M = 0.227$, $SE = 0.027$) (pairwise $p = 0.155$) and mid-test to post-test (pairwise $p = 0.507$) were not significant. For bilateral lateral FEF, there were no main effects of diagnosis or practice group, and there were no interaction effects. See Figure 4.59.

Analysis of bilateral medial FEF revealed a significant effect of time [$F(2, 104) = 7.024$, $p = 0.001$], demonstrated by a significant decrease in activity from pre-test ($M = 0.264$, $SE = 0.014$) to post-test ($M = 0.181$, $SE = 0.019$) (pairwise comparison: $p < 0.001$), and a marginally significant decrease in activity from mid-test ($M = 0.229$, $SE = 0.023$) to post-test (pairwise comparison: $p = 0.060$). The pairwise comparison between activity from pre-test to mid-test was not significant ($p = 0.133$). For bilateral medial FEF, there were no main effects of diagnosis or practice group, and there were no interaction effects. See Figure 4.59.

Analysis of bilateral PFC revealed no significant effects of diagnosis, practice group or time, and there were no interaction effects. Independent samples t-tests, confirmed that there were no significant differences in percent BOLD signal change between the normal and schizophrenia groups at pre-test ($p = 0.480$), mid-test ($p = 0.475$), or post-test ($p = 0.675$) (See Figure 4.64). In the normal group, the change in activity in bilateral PFC did not reveal a significant effect of time [$F(2, 56) = 1.544$, $p = 0.223$]. Further analyses, however, revealed that the decrease in percent BOLD signal change was marginally significant from pre-test ($M = 0.186$, $SD = 0.17$) to post-test ($M = 0.100$, $SD = 0.15$) ($p = 0.60$), but not from pre-test to mid-test ($M = 0.181$, $SD = 0.27$) ($p = 0.938$) or from mid-test to post-test ($p = 0.208$). In the schizophrenia group, the change in activity in bilateral PFC did not reveal a significant effect of time [$F(2, 56) = 0.265$, $p = 0.768$]. Although the trend appears to be decreasing percent BOLD signal change over time, further analyses revealed no significant changes from pre-test ($M = 0.153$, $SD = 0.16$) to post-test ($M = 0.120$, $SD = 0.18$) ($p = 0.450$), from pre-test to mid-test ($M = 0.135$, $SD = 0.19$) ($p = 0.759$) or from mid-test to post-test ($p = 0.450$). Further analyses revealed that for the normal antisaccade practice group, there was not a significant effect of time in antisaccade-related PFC activity [$F(2,26) = 1.535$, $p = 0.234$] (See Figure 4.75). Paired sampled t-tests, however, revealed a significant decrease in activity from pre-test ($M = 0.200$, $SD = 0.125$) to post-test ($M = 0.055$, $SD = 0.149$) [$t(13) = 2.551$, $p = 0.024$], but there was not a significant change between pre-test to mid-test ($p = 0.851$) or between mid-test to post-test ($p = 0.261$). For the normal prosaccade practice group, there was not a significant effect of time in antisaccade-related PFC activity [$F(2,28) = 0.192$, $p = 0.826$] (See Figure 4.76). Paired sampled t-tests revealed no significant

change between pre-test to mid-test (p = 0.890), between mid-test to post-test (p = 0.591), or between pre-test to post-test (p = 0.645). For the schizophrenia antisaccade practice group, there was not a significant effect of time in antisaccade-related PFC activity [F(2,24) = 0.149, p = 0.863] (See Figure 4.75). Paired sampled t-tests revealed no significant change between pre-test to mid-test (p = 0.654), between mid-test to post-test (p = 0.927), or between pre-test to post-test (p = 0.702). Finally, for the schizophrenia prosaccade practice group, there was not a significant effect of time in antisaccade-related PFC activity [F(2,26) = 0.140, p = 0.870] (See Figure 4.76). Paired sampled t-tests revealed no significant change between pre-test to mid-test (p = 0.871), between mid-test to post-test (p = 0.775), or between pre-test to post-test (p = 0.485). It should also be noted that between the schizophrenia prosaccade practice group and the schizophrenia antisaccade practice group, there was a marginally significant difference in PFC signal collapsed across time (p = 0.073), demonstrated as higher signal in the prosaccade practice group (M = 0.176, SE = 0.31) compared to the antisaccade practice group (M = 0.093, SE = 0.032).

Analysis of bilateral IFC revealed a marginally significant effect of diagnosis [F(1, 52) = 2.806, p = 0.100], shown as greater percent signal change for the normal (M = 0.161, SE = 0.026) compared to the schizophrenia group (M = 0.098, SE = 0.027). For bilateral IFC, there were no main effects of practice group or time, and there were no interaction effects. See Figure 4.60.

Analysis of left precuneus revealed a significant effect of time [F(2, 104) = 5.242, p = 0.007], demonstrated by a significant decrease in activity from pre-test (M = 0.285, SE = 0.024) to post-test (M = 0.205, SE = 0.019) (pairwise comparison: p = 0.002), and

from mid-test (M = 0.281, SE = 0.027) to post-test (pairwise comparison: p = 0.012). The pairwise comparison between activity from pre-test to mid-test was not significant (p = 0.909). For left precuneus, there were no main effects of diagnosis or practice group, and there were no interaction effects. See Figure 4.59.

Analysis of left IPL revealed a significant effect of time [F(2, 104) = 3.290, p = 0.041], demonstrated by a significant decrease in activity from pre-test (M = 0.157, SE = 0.022) to post-test (M = 0.085, SE = 0.024) (pairwise comparison: p = 0.014), and a marginally significant decrease in activity from mid-test (M = 0.147, SE = 0.028) to post-test (pairwise comparison: p = 0.061). The pairwise comparison between activity from pre-test to mid-test was not significant (p = 0.753). For left IPL, there were no main effects of diagnosis or practice group, and there were no interaction effects. See Figure 4.59.

Analysis of right IPL revealed a marginally significant effect of practice group [F(1, 52) = 3.858, p = 0.055], shown as greater percent signal change for the prosaccade (M = 0.155, SE = 0.026) compared to the antisaccade practice group (M = 0.083, SE = 0.027). For right IPL, there were no main effects of diagnosis or time, and there were no interaction effects. See Figure 4.61.

Analysis of bilateral striatum revealed a significant effect of diagnosis [F(1, 52) = 5.639, p = 0.021], shown as greater percent signal change for the normal (M = 0.131, SE = 0.014) compared to the schizophrenia group (M = 0.082, SE = 0.015). For bilateral striatum, there were no main effects of practice group or time, and there were no interaction effects. See Figure 4.60.

Analysis of bilateral IFG (BA 44) revealed a marginally significant effect of time [$F(2, 104) = 2.542$, $p = 0.084$], demonstrated by a significant decrease in activity from pre-test ($M = 0.160$, $SE = 0.017$) to post-test ($M = 0.102$, $SE = 0.020$) (pairwise comparison: $p = 0.013$). The pairwise comparisons between activity from pre-test to mid-test ($M = 0.140$, $SE = 0.022$) (pairwise $p = 0.453$) and mid-test to post-test (pairwise $p = 0.199$) were not significant. For bilateral IFG (BA 44), there were no main effects of diagnosis or practice group, and there were no interaction effects. See Figure 4.59.

Analysis of right precuneus, bilateral cuneus, bilateral MOG, bilateral thalamus, left and right insula, and bilateral cerebellum revealed no significant effects of diagnosis, practice group or time, and there were no interaction effects. For graphs comparing all ROIs between all timepoints for the normal and schizophrenia groups, see Figures 4.62-74.

Post-Hoc Analysis

The purpose of the post-hoc analysis was to investigate the behavior of antisaccade-related brain regions over time by correlating task-related BOLD signal change to different sets of reference waves that are specific to a timepoint.

As stated previously, data for the three antisaccade-fixation runs (pre-, mid-, and post-test) were concatenated in space, and Probabilistic ICA (PICA) was performed using MELODIC (Beckmann & Smith, 2004). PICA yielded eight separate components all of which had time courses with the same peak frequency as our experimental design. Components 1, 2, and 4 were most associated with the pre-test session, components 3 and 5 were most associated with the mid-test session, and components 6, 7, and 8 were most associated with the post-test session (See Figures 4.48-50).

Pre-Test Components Analysis

The first portion of the post-hoc analysis focuses only on the components associated with the pre-test session, i.e., components 1, 2, and 4. For the *pre-test components* analysis, all datasets were run through three separate GLM analyses. The first GLM used component 1 as the sole reference wave and used the remaining 31 components as noise and/or motion regressors (components 2, 3, 4, 5, 6, 7, and 8 plus the 24 non-task-related components). The second GLM used component 2 as the sole reference wave and used the remaining 31 components as noise and/or motion regressors (components 1, 3, 4, 5, 6, 7, and 8 plus the 24 non-task-related components). The third GLM used component 4 as the sole reference wave and used the remaining 31 components as noise and/or motion regressors (components 1, 2, 3, 5, 6, 7, and 8 plus the 24 non-task-related components). For each GLM (3 total), for each timepoint (3), a one-sample t-test versus 0 was conducted to determine which areas of the brain showed BOLD signal change related to the experimental task for the antisaccade-fixation run. After applying to each t-map (9 total) a threshold/cluster method derived from Monte Carlo simulations (Ward, 2000) to protect against false positives, each map was converted to color maps. The pre-, mid-, and post-test maps that were run through the first GLM (with component 1 as the reference wave) were converted to *red*. The pre-, mid-, and post-test maps that were run through the second GLM (with component 2 as the reference wave) were converted to *green*. The pre-, mid-, and post-test maps that were run through the third GLM (with component 4 as the reference wave) were converted to *blue*. Finally for each timepoint, the separate color maps (respective to separate GLMs) were combined. The resulting colormaps denote the following; regions

associated only with PICA component 1 are shown in *red*, regions associated only with PICA component 2 are shown in *green*, regions associated only with PICA component 4 are shown in *blue*, regions associated with both PICA components 1 and 2 are shown in *yellow*, regions associated with both PICA components 1 and 4 are shown in *pink*, regions associated with both PICA components 2 and 4 are shown in *aqua*, and regions associated with PICA components 1, 2, and 3 are shown in *white*. For a colormap of pre-test data see Figure 4.77, for a colormap of mid-test data see Figure 4.78, and for a colormap of post-test data see Figure 4.79.

Mid-Test Components Analysis

The second portion of the post-hoc analysis focuses only on the components associated with the mid-test session, i.e., components 3 and 5. For the *mid-test components* analysis, all datasets were run through two separate GLM analyses. The first GLM used component 3 as the sole reference wave and used the remaining 31 components as noise and/or motion regressors (components 1, 2, 4, 5, 6, 7, and 8 plus the 24 non-task-related components). The second GLM used component 5 as the sole reference wave and used the remaining 31 components as noise and/or motion regressors (components 1, 2, 3, 4, 6, 7, and 8 plus the 24 non-task-related components). For each GLM (2 total), for each timepoint (3), a one-sample t-test versus 0 was conducted to determine which areas of the brain showed BOLD signal change related to the experimental task for the antisaccade-fixation run. After applying to each t-map (6 total) a threshold/cluster method derived from Monte Carlo simulations (Ward, 2000) to protect against false positives, each map was converted to color maps. The pre-, mid-, and post-

test maps that were run through the first GLM (with component 3 as the reference wave) were converted to *red*. The pre-, mid-, and post-test maps that were run through the second GLM (with component 5 as the reference wave) were converted to *green*. Finally, for each timepoint, the separate color maps (respective to separate GLMs) were combined. The resulting colormaps denote the following; regions associated only with PICA component 3 are shown in *red*, regions associated only with PICA component 5 are shown in *green*, and regions associated with both PICA components 3 and 5 are shown in *yellow*. For a colormap of pre-test data see Figure 4.80, for a colormap of mid-test data see Figure 4.81, and for a colormap of post-test data see Figure 4.82.

Post-Test Components Analysis

The third portion of the post-hoc analysis focuses only on the components associated with the post-test session, i.e., components 6, 7 and 8. For the *post-test components* analysis, all datasets were run through a similar procedure as that specified in the *pre-test components* analysis section. For a colormap of pre-test data see Figure 4.83, for a colormap of mid-test data see Figure 4.84, and for a colormap of post-test data see Figure 4.85.

FMRI & Behavioral Data Correlations

The eyetrack data collected during the antisaccade-fixation runs during pre-test, mid-test, and post-test were analyzed for significant correlations with the ROI percent signal change data respective to each run.

Pre-Test Correlations

For percent of correct trials during the antisaccade-fixation run during pre-test, correlation analyses revealed the following: For all subjects, there were no significant correlations. For the normal group, there were no significant correlations. For the schizophrenia group, percent of correct trials was negatively associated with activity in left precuneus ($r = -0.412$, $p = 0.036$) and negatively associated with activity in bilateral middle occipital gyrus ($r = -0.422$, $p = 0.031$). For the prosaccade practice group, percent of correct trials was negatively associated with activity in bilateral inferior frontal gyrus, BA 44 ($r = -0.382$, $p = 0.044$). For antisaccade practice group, there were no significant correlations.

For reaction time of correct trials during the antisaccade-fixation run during pre-test, correlation analyses revealed the following: For all subjects, reaction time of correct antisaccades was negatively associated with activity in right precuneus ($r = -0.283$, $p = 0.046$). For the normal group, the schizophrenia group, the prosaccade practice group, and the antisaccade practice group, there were no significant correlations.

Mid-Test Correlations

For percent of correct trials during the antisaccade-fixation run during mid-test, correlation analyses revealed the following: For all subjects, percent of correct trials was negatively associated with activity in bilateral cuneus ($r = -0.343$, $p = 0.014$). For the normal group, there were no significant corellations. For the schizophrenia group, percent of correct trials was negatively associated with activity in bilateral cuneus ($r = -0.544$, $p = 0.005$), negatively associated with activity in bilateral middle occipital gyrus ($r = -0.447$, $p = 0.028$), and negatively associated with activity in bilateral inferior frontal

gyrus, BA 44 (r = -0.548, p = 0.005). For the prosaccade practice group, percent of correct trials was negatively associated with activity in bilateral PFC (r = -0.464, p = 0.014), negatively associated with activity in bilateral IFC (r = -0.414, p = 0.031), negatively associated with activity in bilateral cuneus (r = -0.476, p = 0.012), negatively associated with activity in left IPL (r = -0.387, p = 0.046), negatively associated with activity in bilateral MOG (r = -0.430, p = 0.025), and negatively associated with activity in bilateral striatum (r = -0.409, p = 0.033). For the antisaccade practice group, there were no significant corellations.

For reaction time of correct trials during the antisaccade-fixation run during mid-test, analyses revealed no significant correlations for all subjects, the normal group, the schizophrenia group, the prosaccade practice group, or the antisaccade practice group.

Post-Test Correlations

For percent of correct trials during the antisaccade-fixation run during post-test, correlation analyses revealed the following: For all subjects, percent of correct trials was negatively associated with activity in bilateral cuneus (r = -0.298, p = 0.035). For the normal group, percent of correct trials was negatively associated with activity in left IPL (r = -0.439, p = 0.027). For the schizophrenia group, percent of correct trials was negatively associated with activity in bilateral thalamus (r = -0.413, p = 0.044), and negatively associated with activity in bilateral cerebellum (r = -0.438, p = 0.032). For the prosaccade and antisaccade practice groups, there were no significant correlations.

For reaction time of correct trials during the antisaccade-fixation run during post-test, correlation analyses revealed the following: For all subjects, reaction time of correct antisaccades was negatively associated with activity in bilateral IFC (r = -0.349, p =

0.013), negatively associated with activity in right IPL (r = -0.309, p = 0.030), and negatively associated with activity in bilateral MOG (r = -0.292, p = 0.041). For the normal group, there were no significant correlations. For the schizophrenia group, reaction time of correct antisaccades was negatively associated with activity in bilateral cuneus (r = -0.404, p = 0.049) and negatively associated with activity in left insula (r = -0.477, p = 0.018). For the prosaccade practice group, reaction time of correct antisaccades was negatively associated with activity in SEF (r = -0.412, p = 0.036), negatively associated with activity in bilateral PFC (r = -0.443, p = 0.023), negatively associated with activity in bilateral IFC (r = -0.574, p = 0.002), negatively associated with activity in right IPL (r = -0.509, p = 0.007), negatively associated with activity in bilateral striatum (r = -0.618, p < 0.001), negatively associated with activity in bilateral IFG, BA 44 (r = -0.403, p = 0.040), negatively associated with activity in left insula (r = -0.438, p = 0.025), and negatively associated with activity in right insula (r = -0.452, p = 0.020). For the antisaccade practice group, there were no significant correlations.

PFC-Specific Behavioral Data Correlations

Per Hypothesis 2b, the following behavioral data were correlated with percent BOLD signal change in bilateral PFC during the antisaccade-fixation task for schizophrenia subjects.

Change in Antisaccade Performance

For schizophrenia participants, correlation analyses were run comparing change in BOLD signal activation in bilateral PFC between pre-test and post-test (i.e., post-test percent BOLD signal change *minus* pre-test percent BOLD signal change) and change in

antisaccade performance between pre-test and post-test (i.e., post-test percent correct for antisaccades *minus* pre-test percent correct for antisaccades). Analyses revealed only a slightly positive correlation ($r = 0.038$, $p = 0.859$), signifying that as PFC activity increases, antisaccade scores only slightly improve. See Figure 4.86.

Change in WCST Performance

For schizophrenia participants, correlation analyses were run comparing change in BOLD signal activation in bilateral PFC between pre-test and post-test and change in various WCST performance parameters between pre-test and post-test. Analyses for percent perseverative errors revealed a marginally significant negative correlation ($r = -0.337$, $p = 0.079$), signifying that as PFC activity increases, perseverate error rates decrease. See Figure 4.87. Analyses for number of trials administered revealed a weak negative correlation ($r = -0.210$, $p = 0.284$), signifying that as PFC activity increases, participants are able to complete the WCST in less trials. Analyses for percentage of errors revealed a weak negative correlation ($r = -0.145$, $p = 0.462$), signifying that as PFC activity increases, error rates decrease. Analyses for percentage of conceptual level responses revealed a weak positive correlation ($r = +0.221$, $p = 0.259$), signifying that as PFC activity increases, percentage of conceptual level responses increases. Analyses for percent of perseverative responses revealed a marginally significant negative correlation ($r = -0.342$, $p = 0.075$), signifying that as PFC activity increases, perseverative response rates decrease. Analyses for percentage of non-perseverative errors revealed a weak positive correlation ($r = +0.157$, $p = 0.424$), signifying that as PFC activity increases, non-perseverative error rates increase. Analyses for number of categories completed

revealed a weak positive correlation (r = +0.186, p = 0.344), signifying that as PFC activity increases, participants complete more WCST categories. Finally, analyses for number of trials to complete the first category revealed a moderate negative correlation (r = -0.308, p = 0.111), signifying that as PFC activity increases, participants complete the first WCST category in fewer trials.

Change in ODRT Performance

For schizophrenia participants, correlation analyses were run comparing change in BOLD signal activation in bilateral PFC between pre-test and post-test and change in various ODRT performance parameters between pre-test and post-test. Analyses for ODRT gain revealed a significant negative correlation (r = -0.431, p = 0.022), signifying that as PFC activity increases, accuracy decreases. See Figure 4.88. Analyses for ODRT number of anticipatory saccades revealed a weak negative correlation (r = -0.171, p = 0.385), signifying that as PFC activity increases, the rate of anticipatory saccades decreases. Analyses for ODRT average number of anticipatory saccades per trial revealed a weak negative correlation (r = -0.115, p = 0.560), signifying that as PFC activity increases, the rate of average anticipatory saccades per trial decreases. Analyses for ODRT percent correct revealed a weak negative correlation (r = -0.106, p = 0.590), signifying that as PFC activity increases, the percent correct of ODRT trials decreases. Analyses for ODRT reaction time revealed a moderate positive correlation (r = +0.303, p = 0.117), signifying that as PFC activity increases, ODRT reaction time for correct responses increases.

Table 4.1

Talairach coordinates of the center of mass for each ROI

ROI	L/R	*X*	*Y*	*Z*
SEF		0	-2	+55
Lat FEF	L	-40	-9	+50
	R	+43	-6	+45
Med FEF	L	-24	-9	+52
	R	+28	-7	+51
PFC	L	-33	+35	+28
	R	+35	+36	+27
IFC	L	-41	+46	+3
	R	+48	+38	+1
Precuneus	L	-22	-62	+47
	R	+20	-66	+48
Cuneus	L	-9	-72	+5
	R	+10	-71	+5
IPL	L	-54	-41	+24
	R	+54	-49	+20
Middle Occ	L	-24	-76	+19
	R	+30	-76	+22
Striatum	L	-22	-3	+10
	R	+22	-2	+11
Thalamus	L	-10	-17	+6
	R	+12	-18	+10
IFG (BA 44)	L	-45	+2	+22
	R	+50	+2	+22
Insula	L	-36	+8	+2
	R	+48	+8	+2
Cerebellum	L	-9	-77	-12
	R	+9	-72	-12

Regions represent areas that showed significant differences in BOLD signal across the three timepoints.

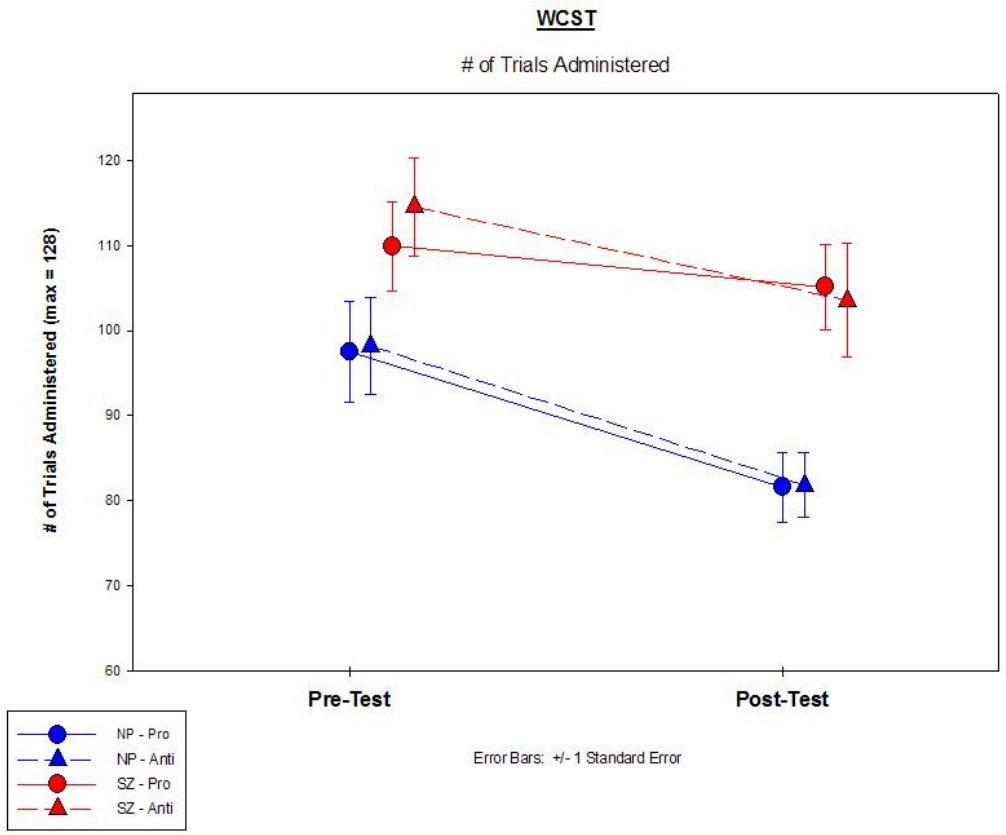


Figure 4.1 WCST: Number of Trials Administered

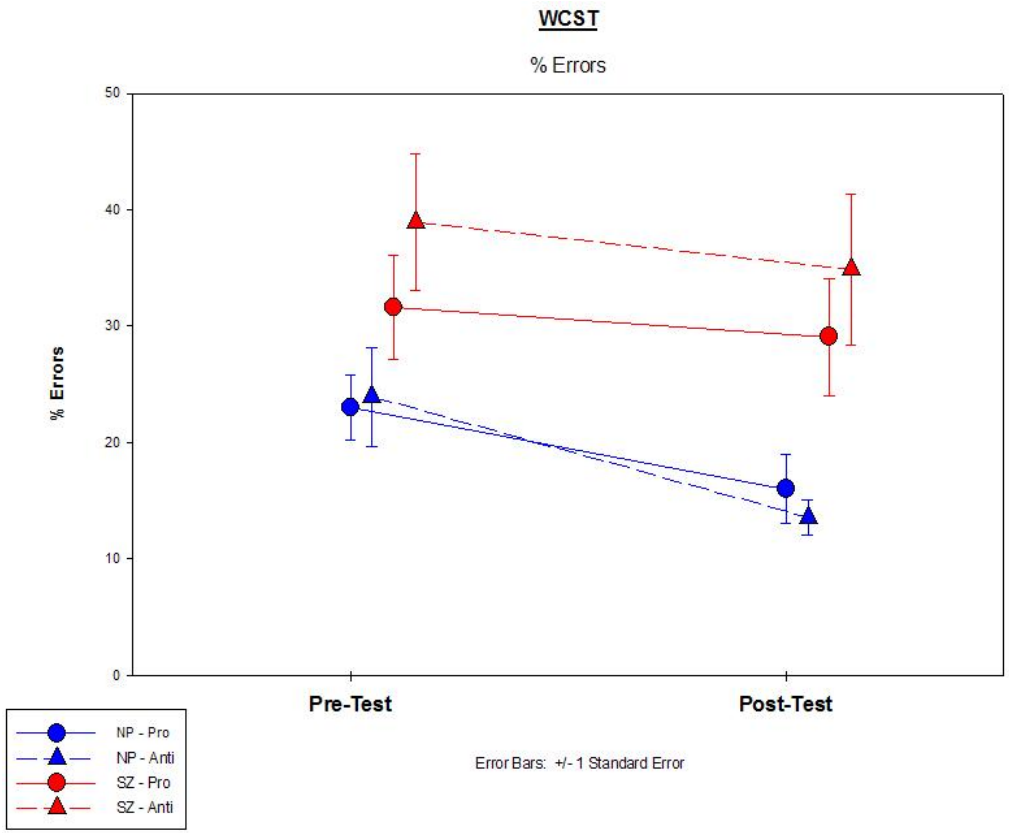


Figure 4.2 WCST: Errors

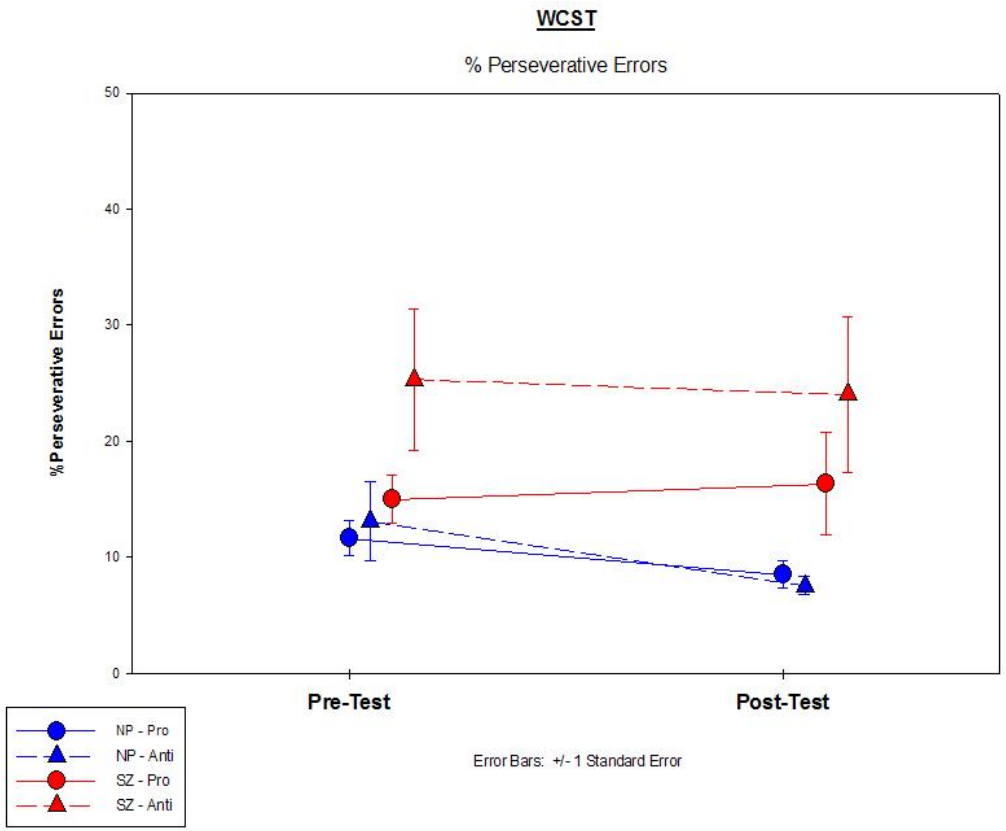


Figure 4.3 WCST: Perseverative Errors

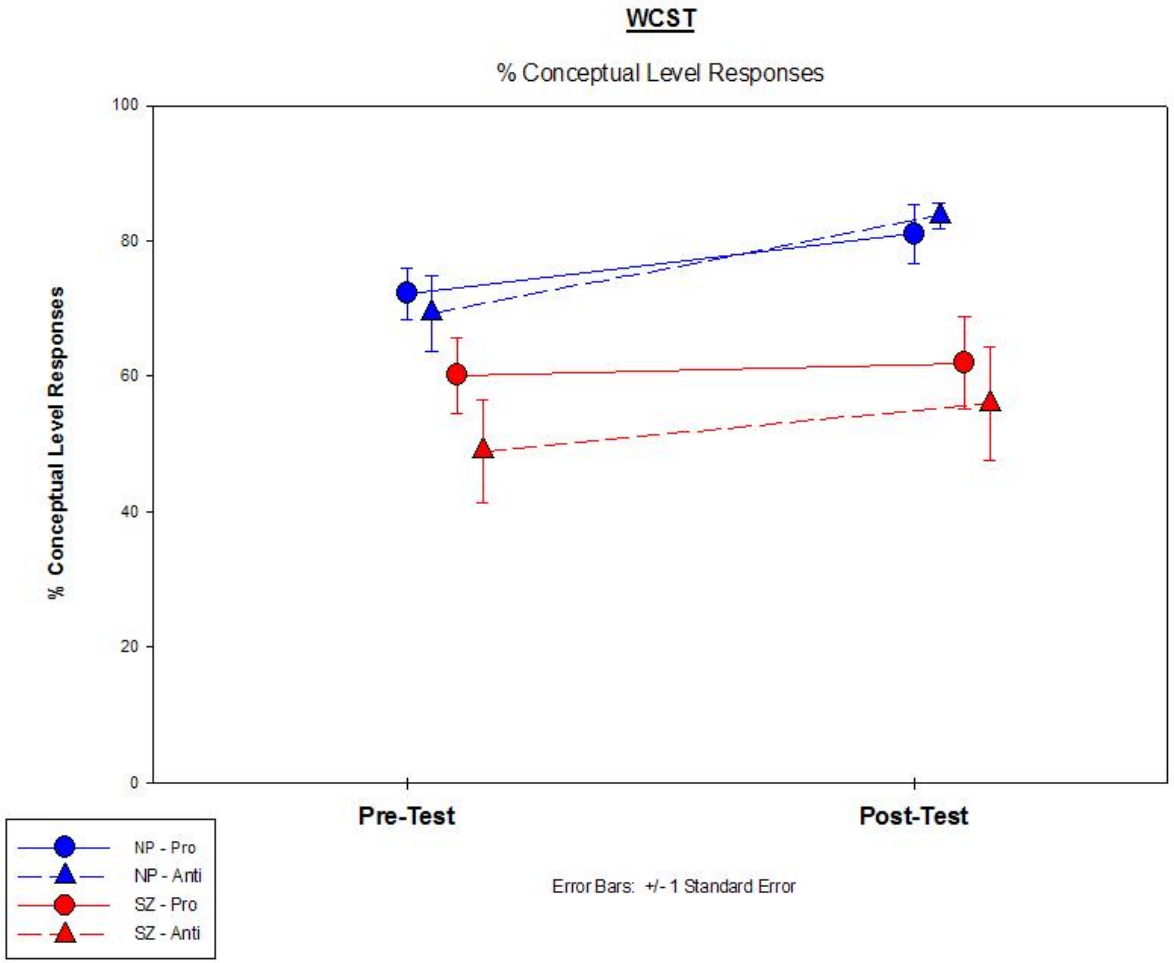


Figure 4.4 WCST: Conceptual Level Responses

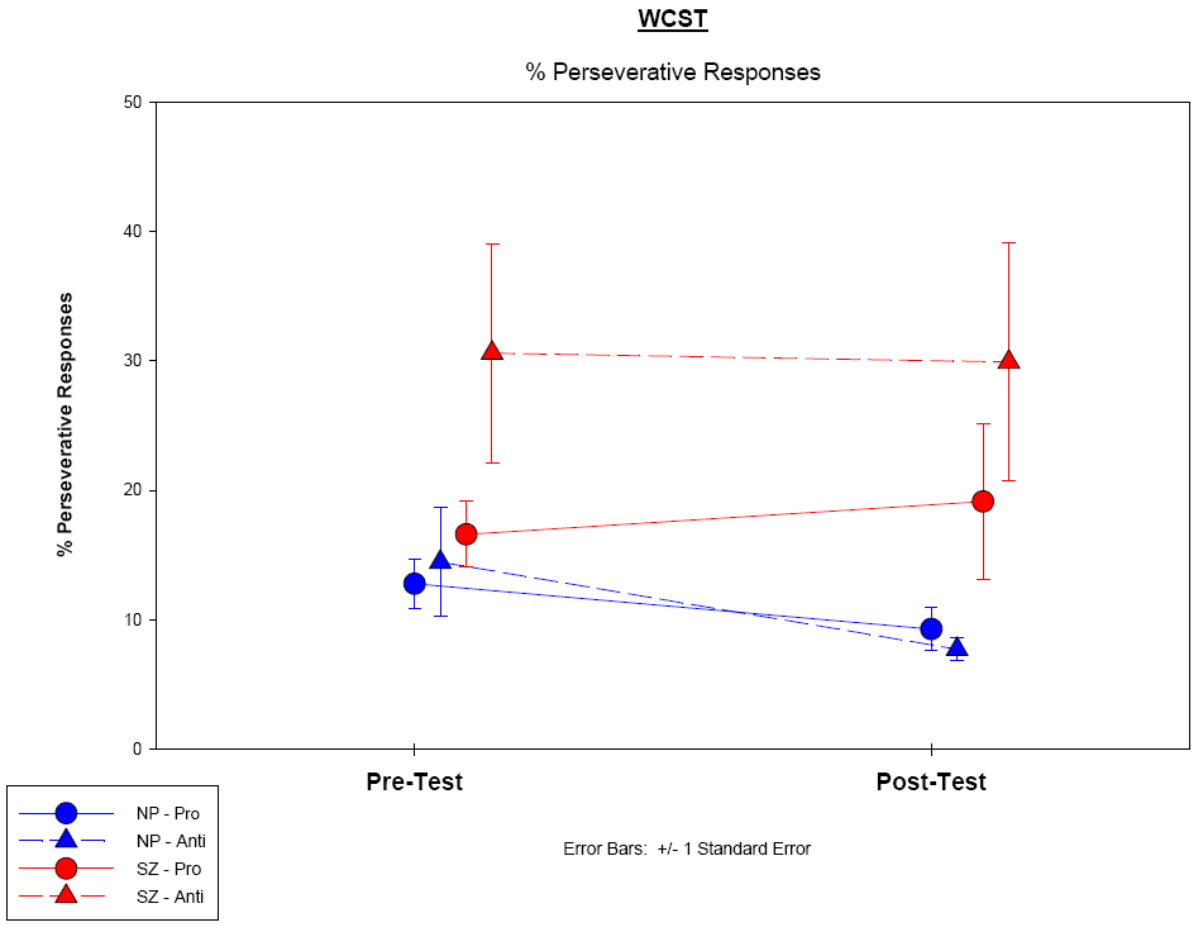


Figure 4.5 WCST: Perseverative Responses

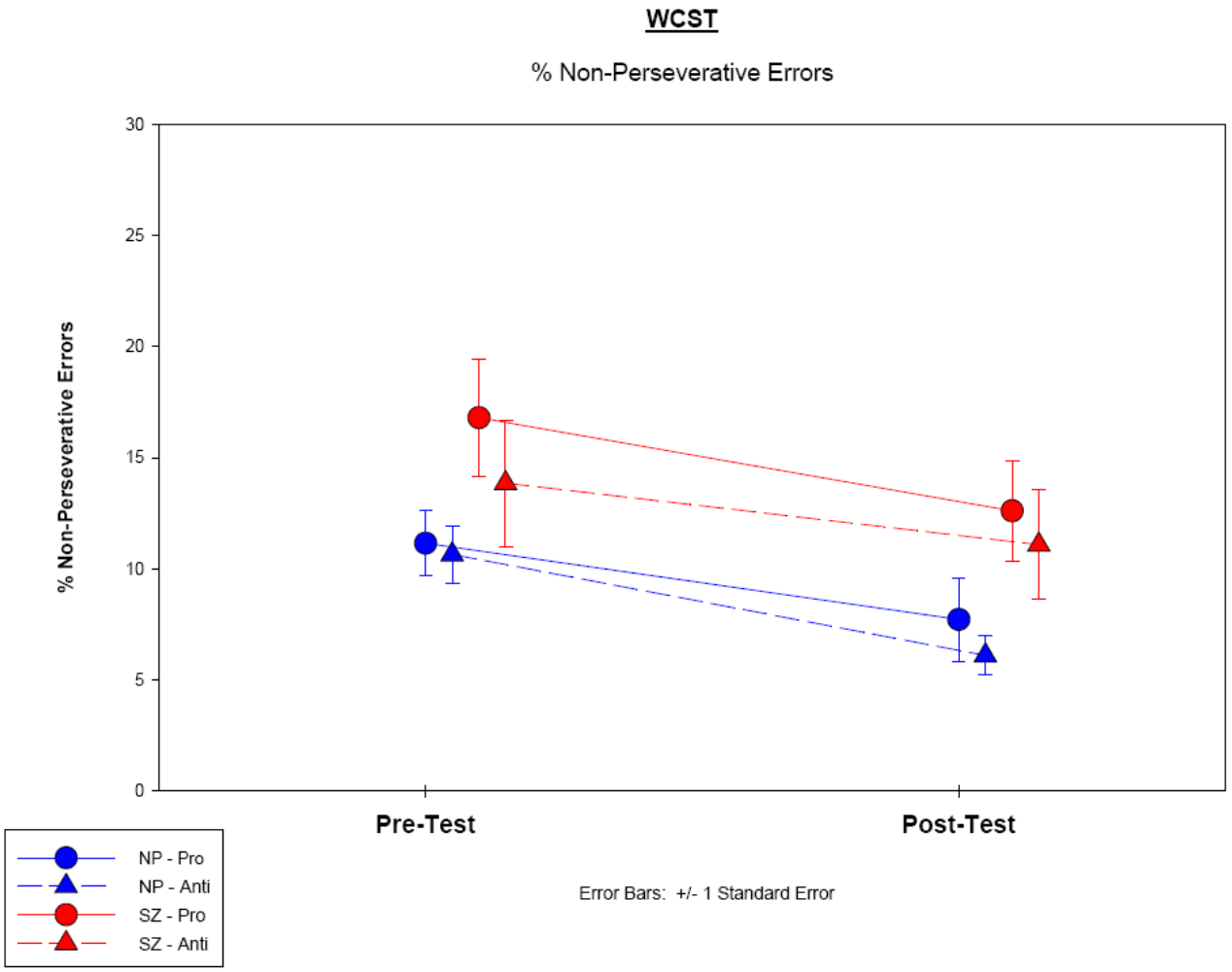


Figure 4.6 WCST: Non-Perseverative Responses

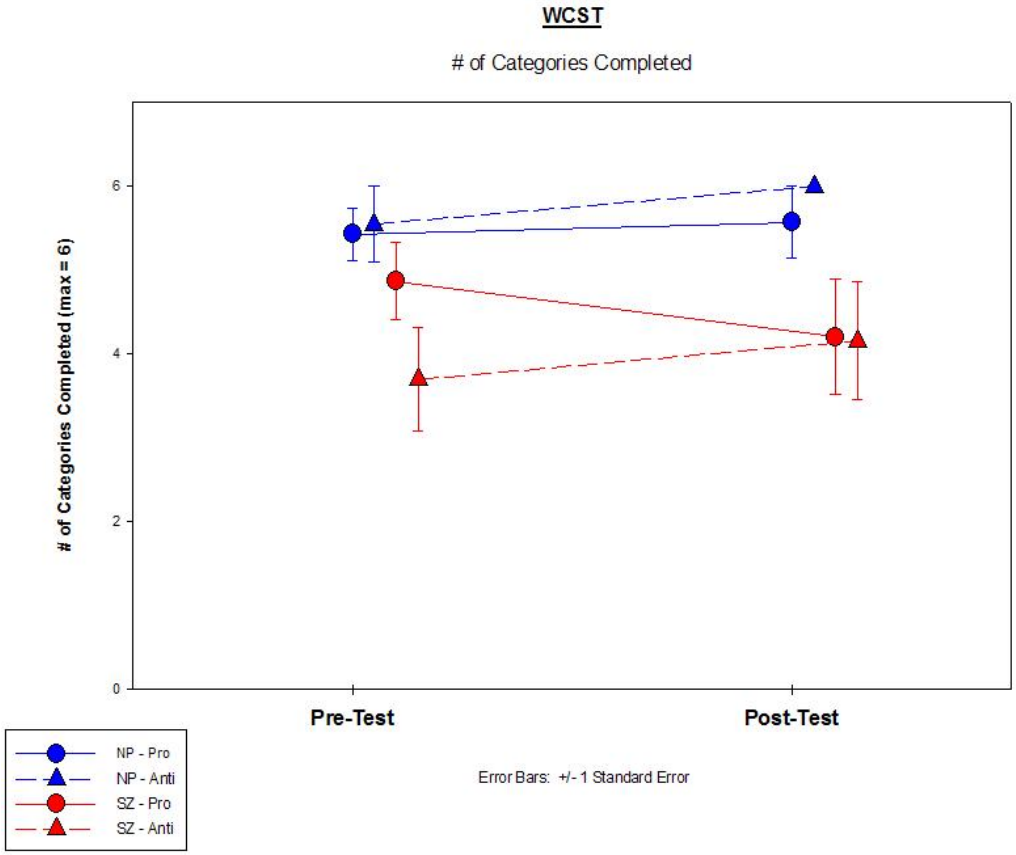


Figure 4.7 WCST: Categories Completed

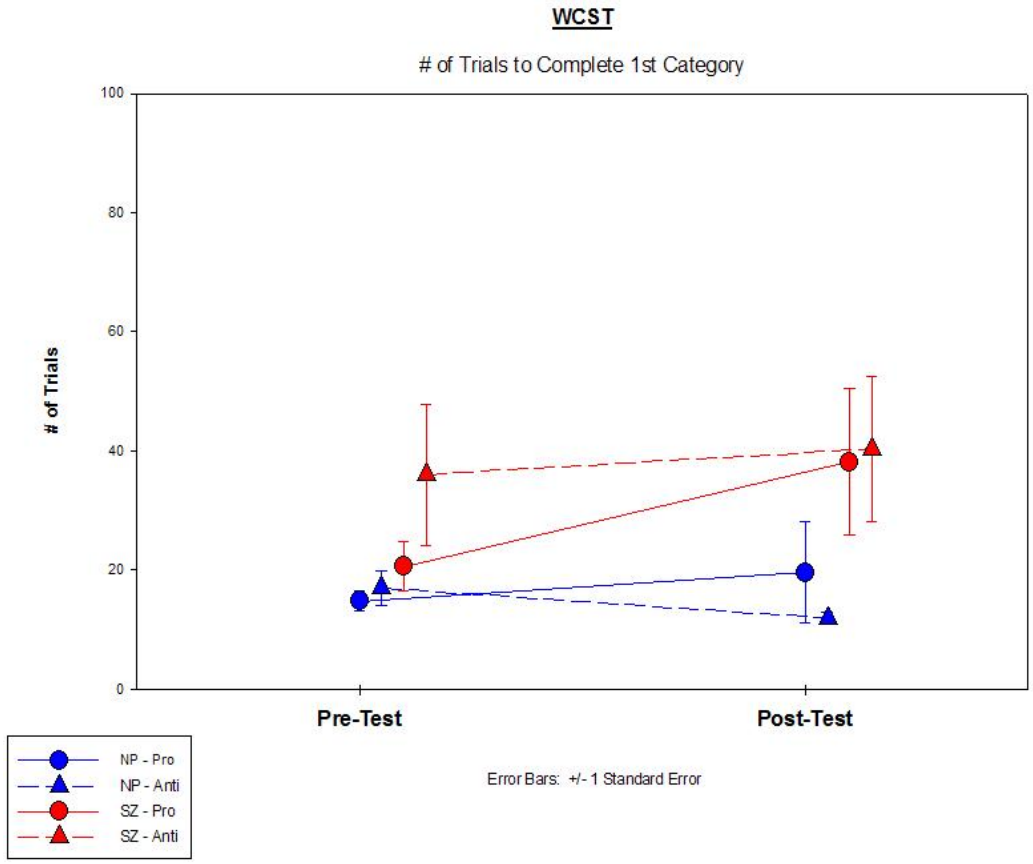


Figure 4.8 WCST: Trials to Complete First Category

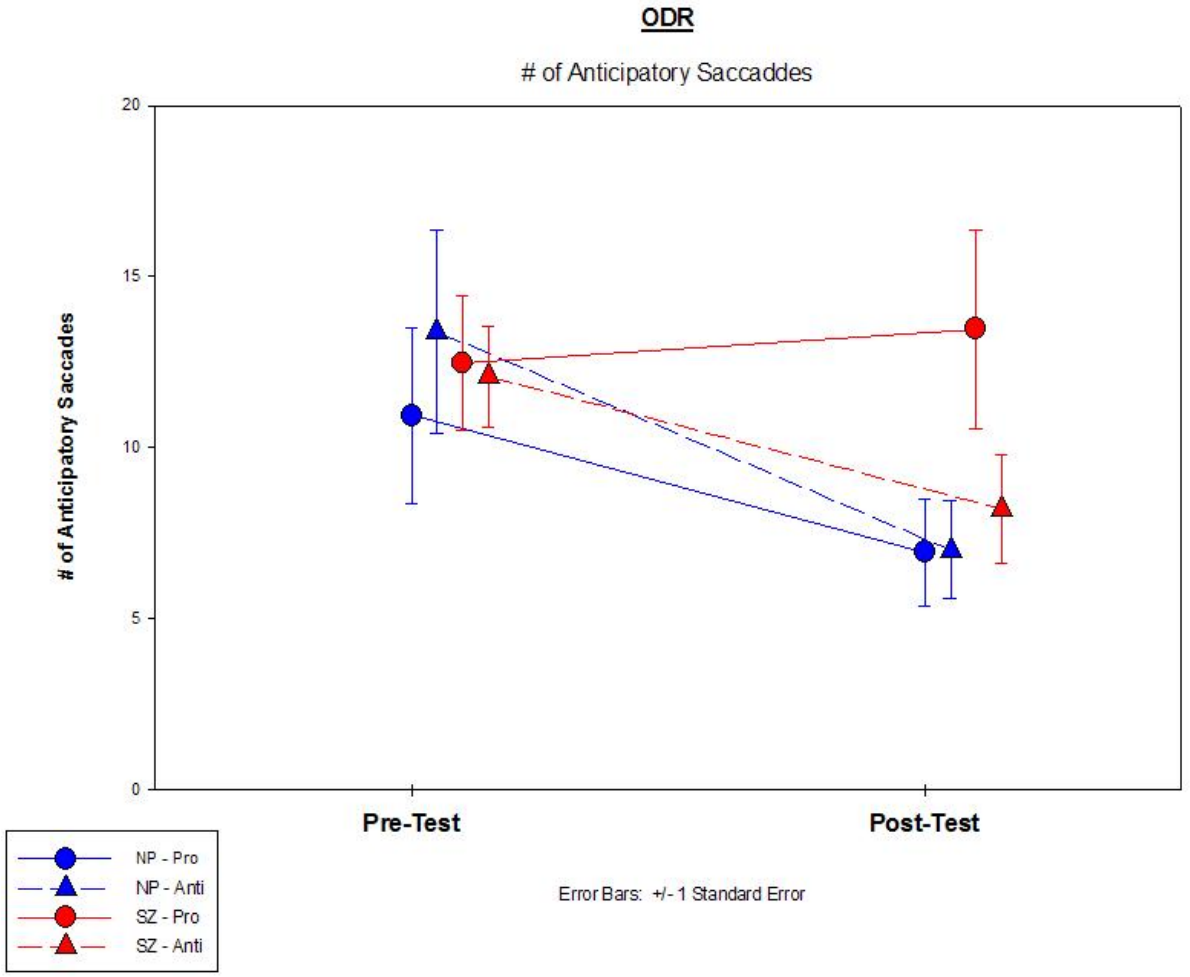


Figure 4.9 ODRT: Number of Anticipatory Saccades

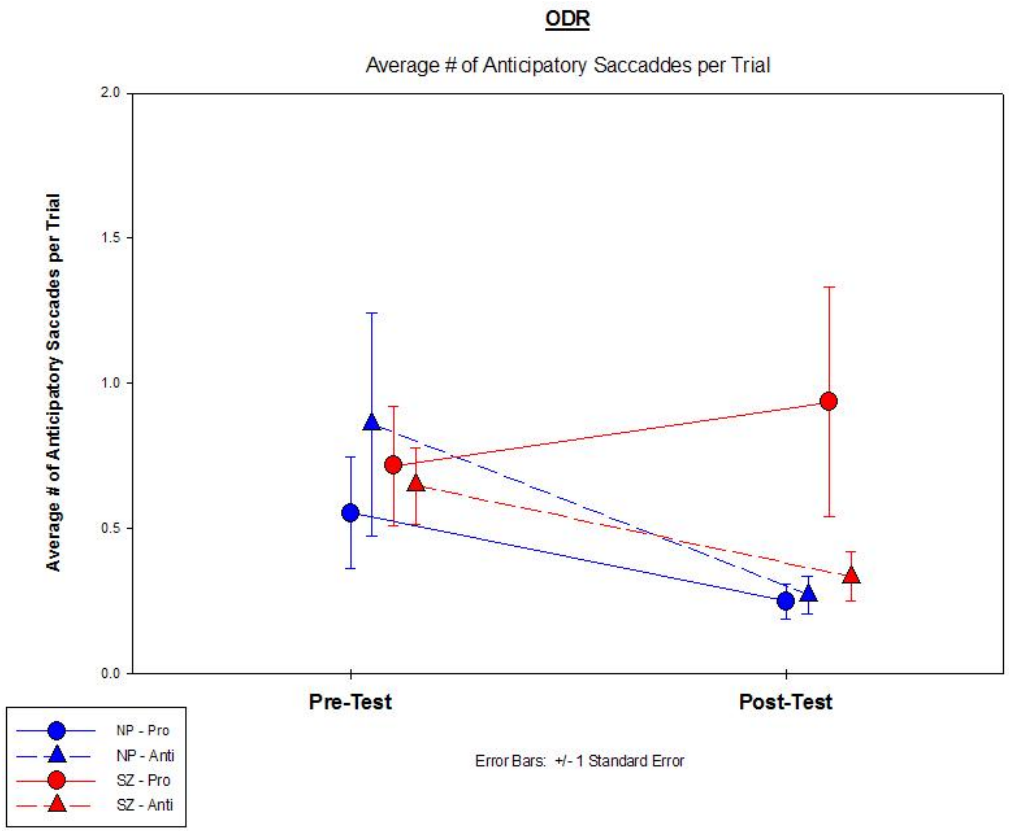


Figure 4.10 ODRT: Average Anticipatory Saccades Per Trial

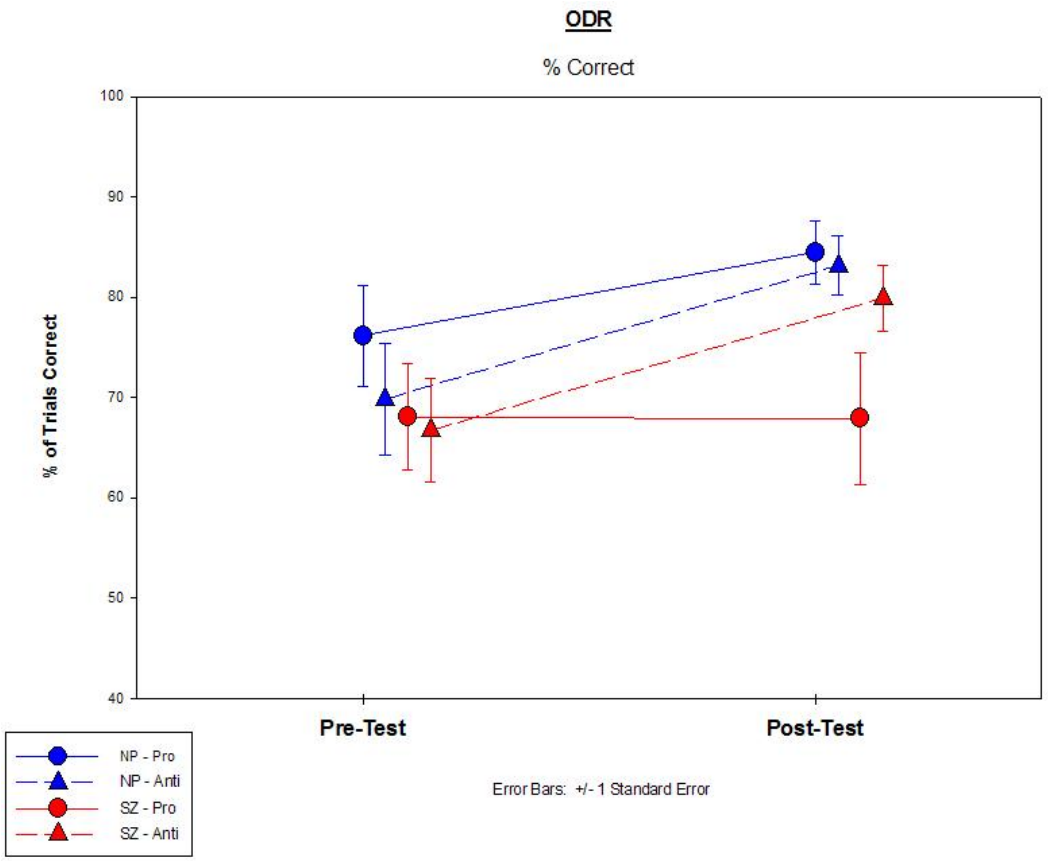


Figure 4.11 ODRT: Percent Correct

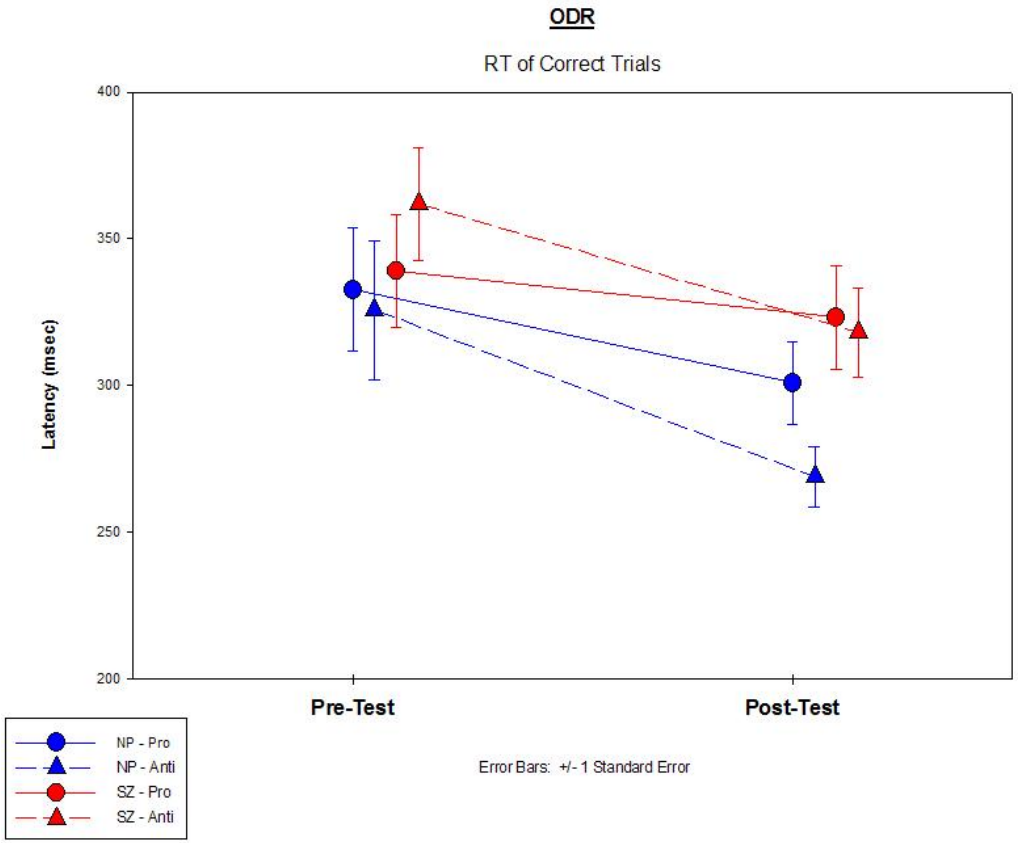


Figure 4.12 ODRT: Reaction Time

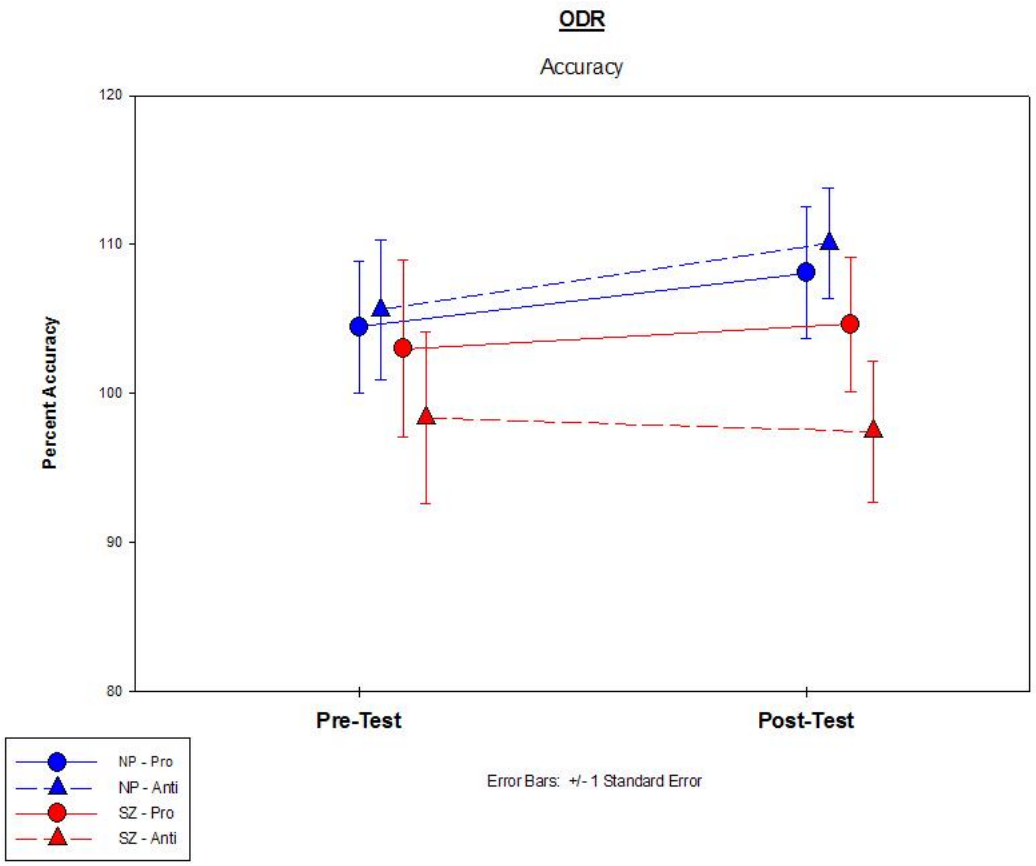


Figure 4.13 ODRT: Accuracy

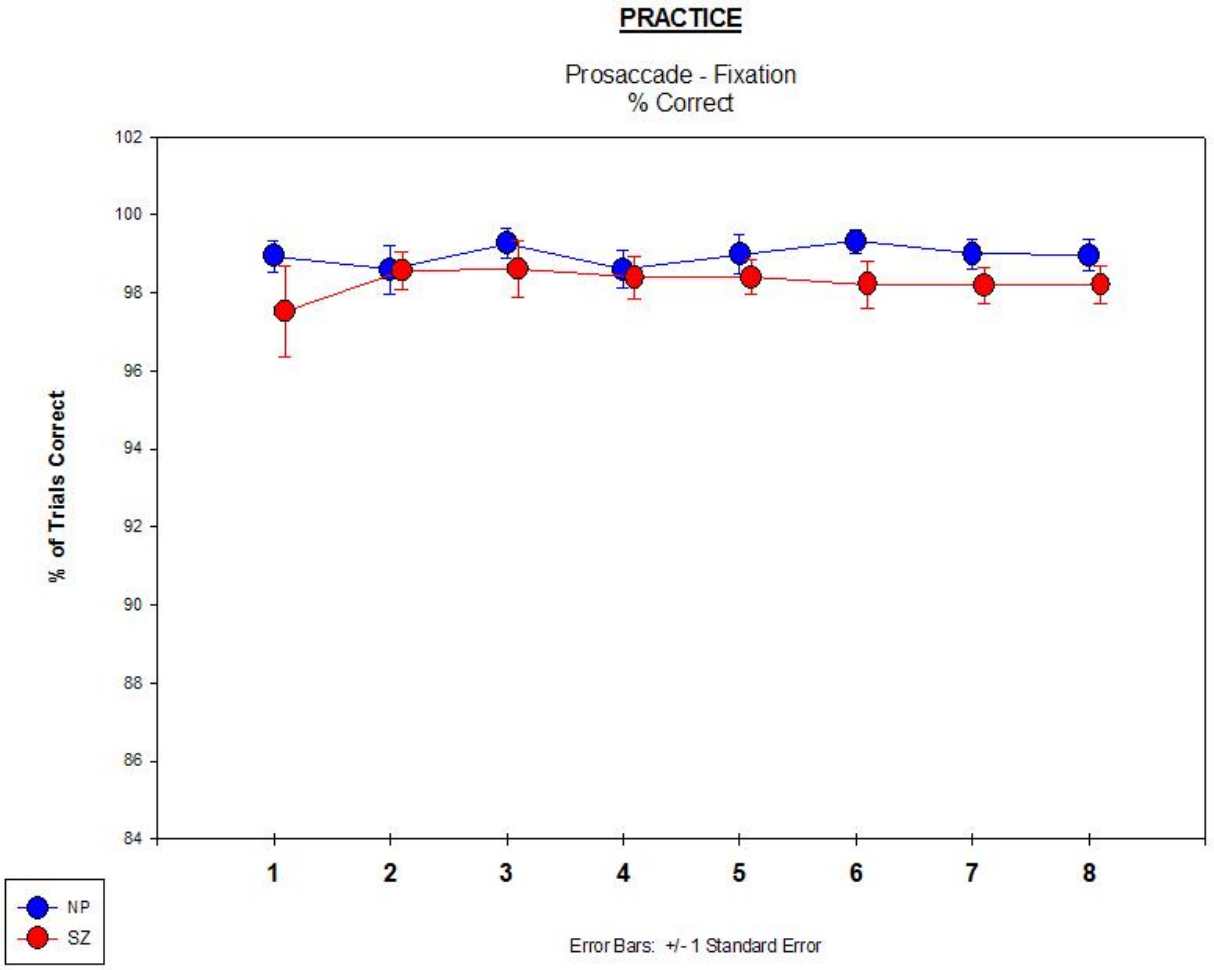


Figure 4.14 Practice Sessions: Prosaccade Percent Correct

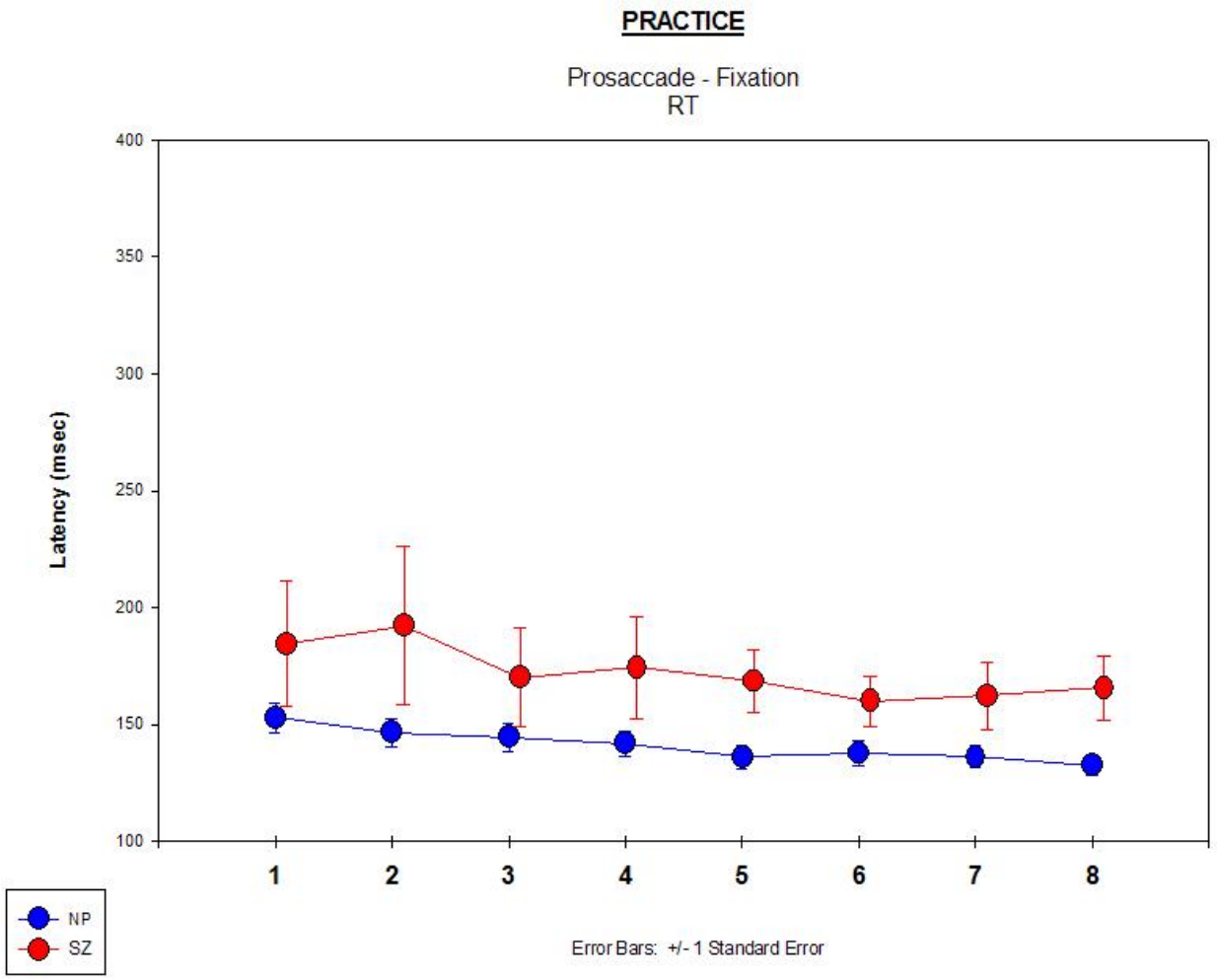


Figure 4.15 Practice Sessions: Prosaccade Latency

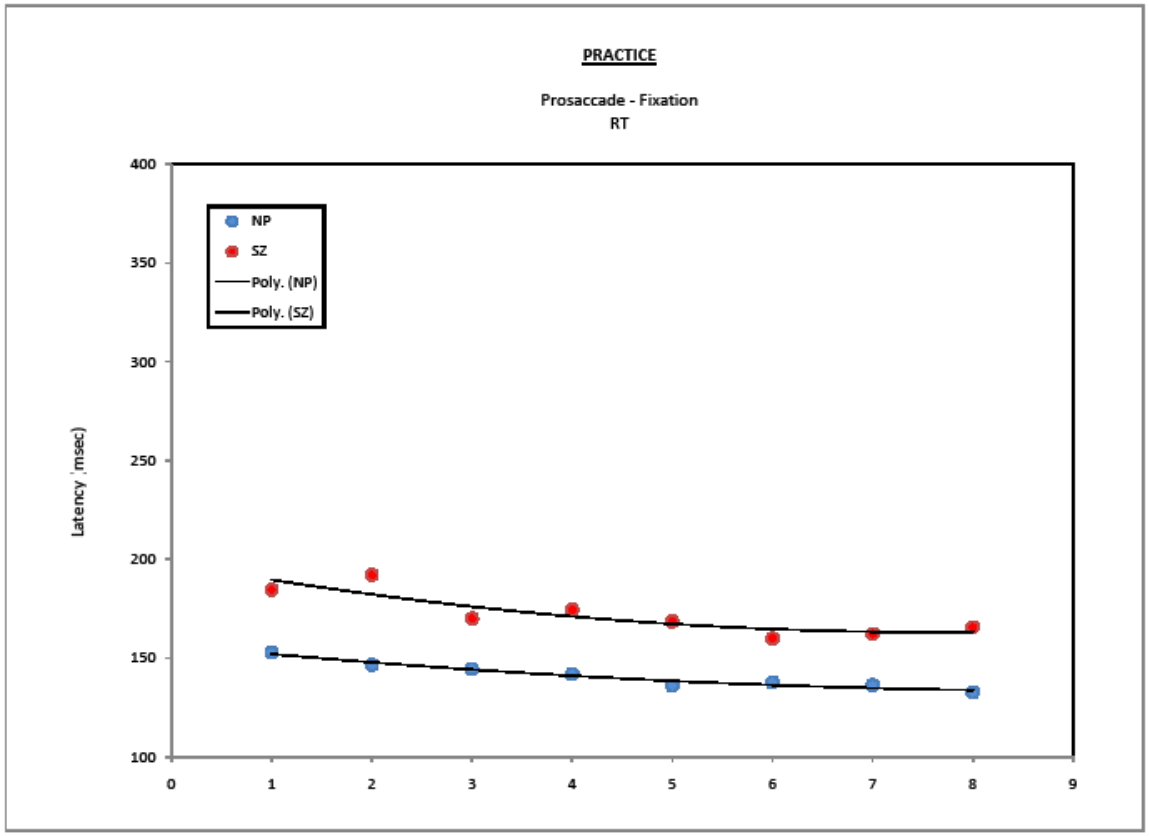


Figure 4.16 Practice Sessions: Prosaccade Latency Curve

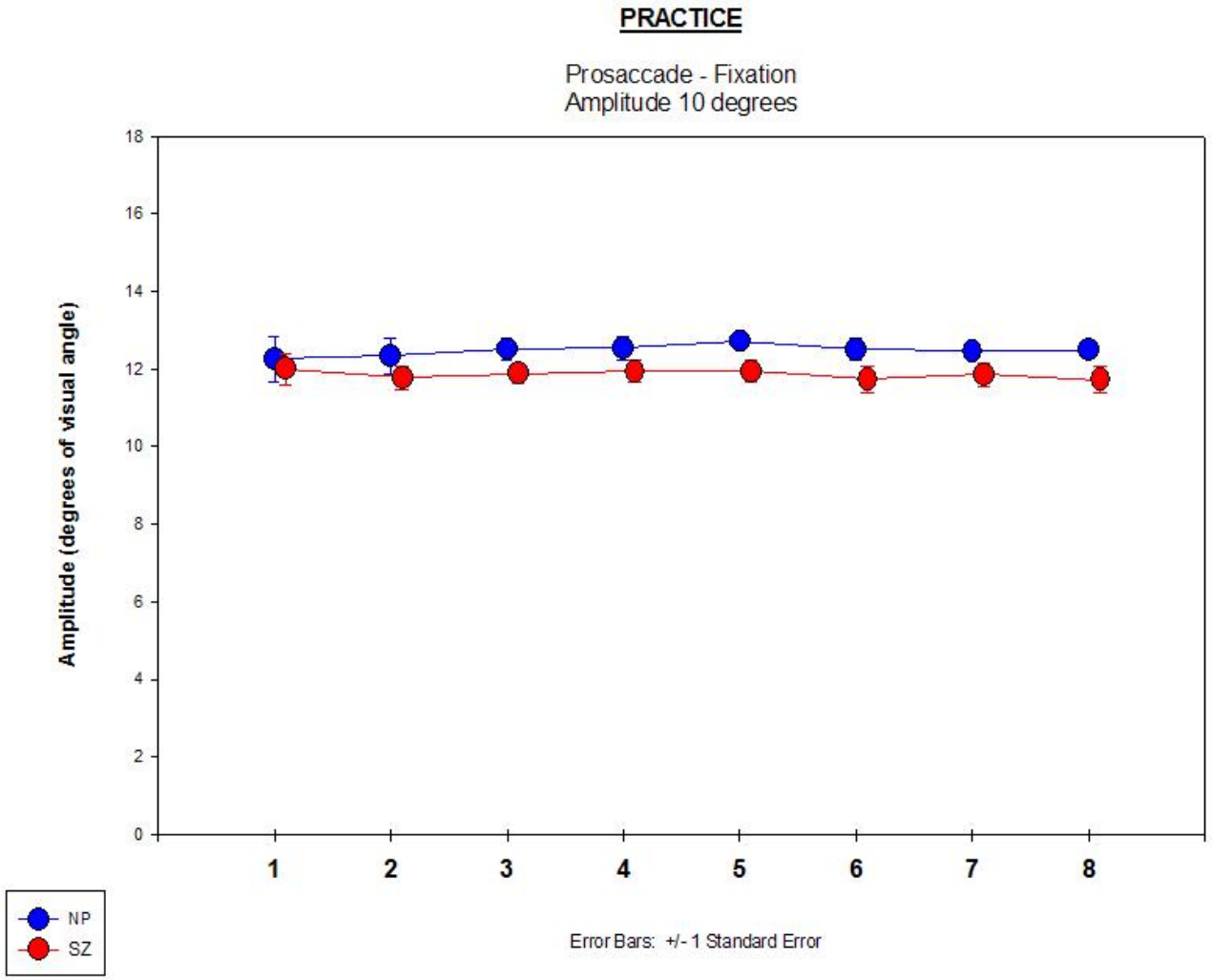


Figure 4.17 Practice Sessions: Prosaccade Accuracy: 10-Degree Eccentricity

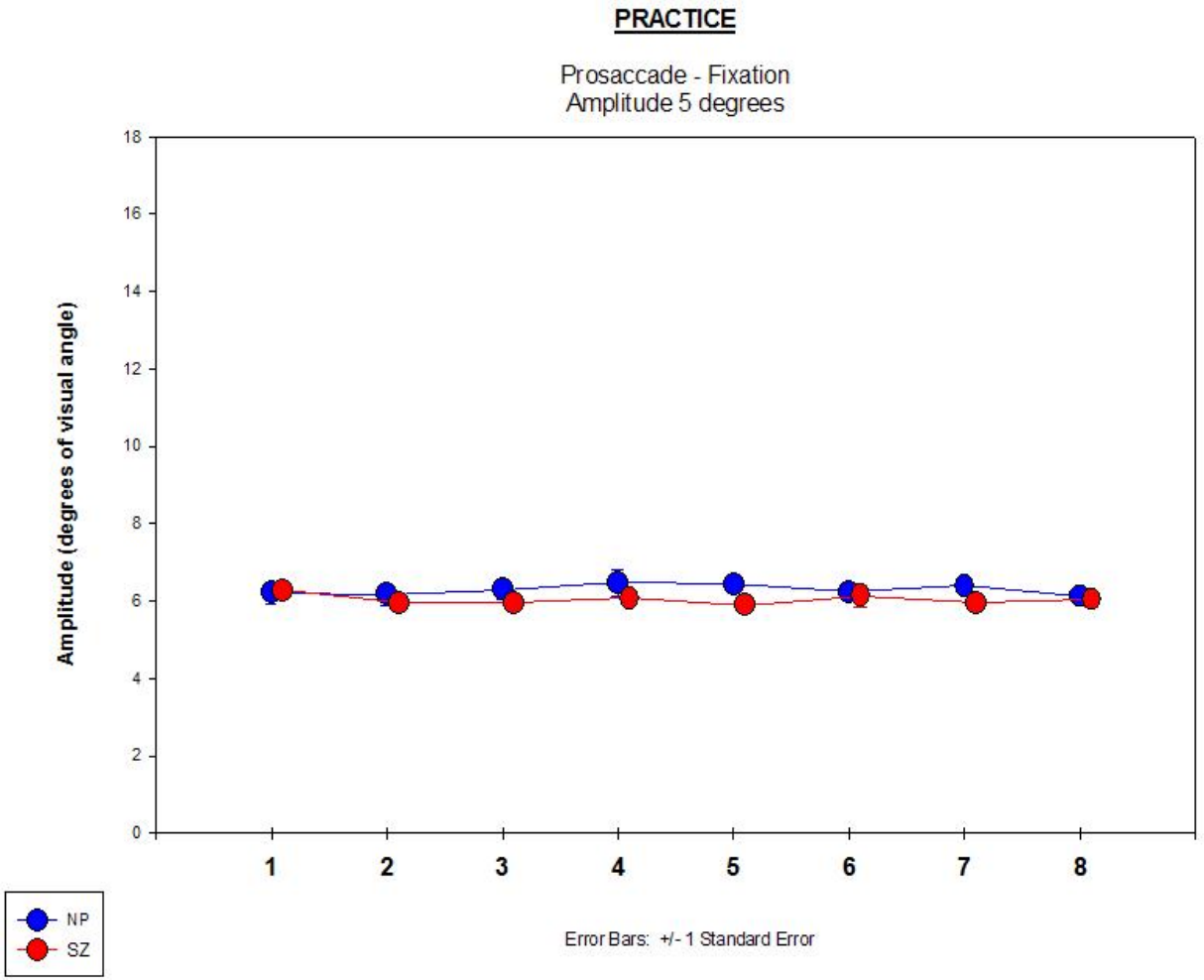


Figure 4.18 Practice Sessions: Prosaccade Accuracy: 5-Degree Eccentricity

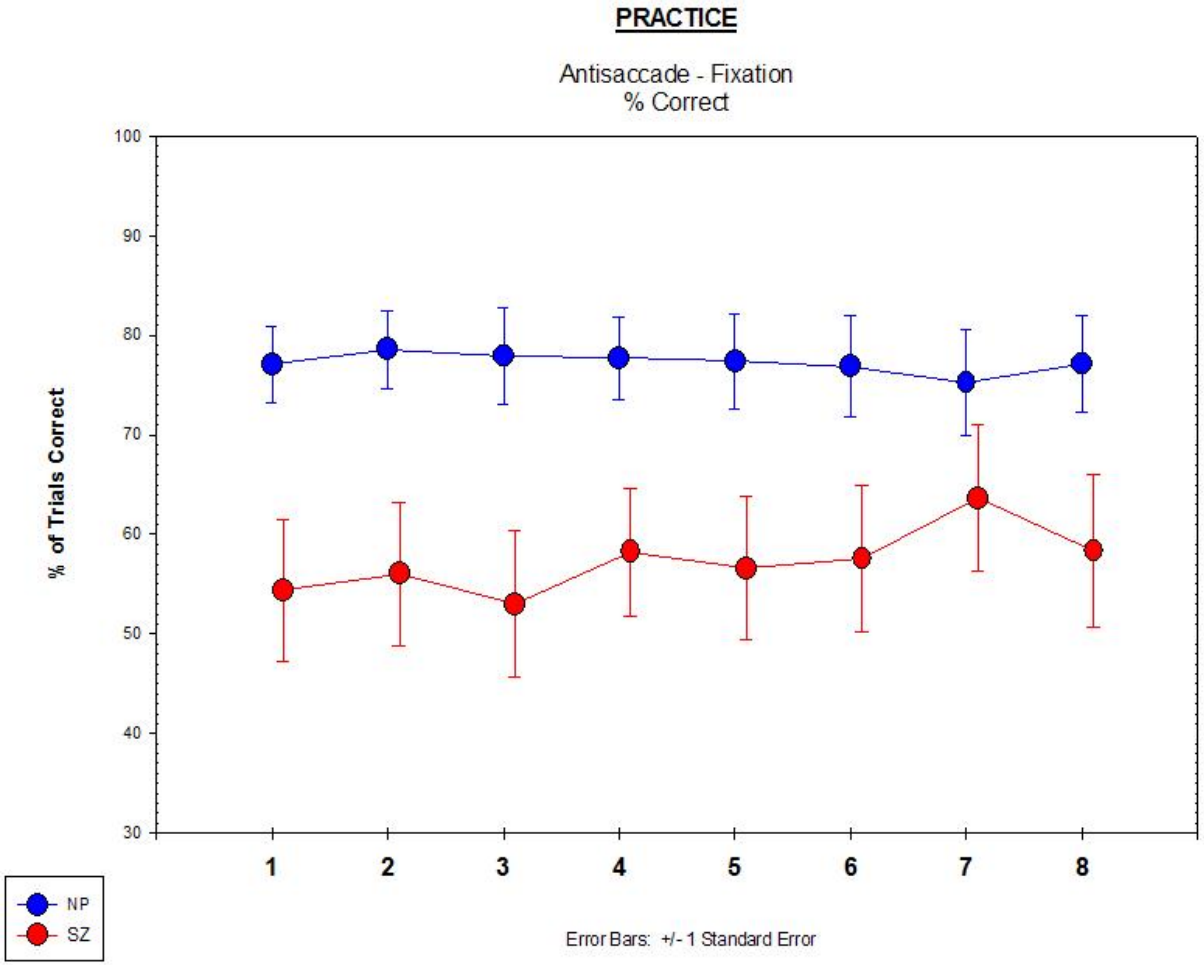


Figure 4.19 Practice Sessions: Antisaccade Percent Correct

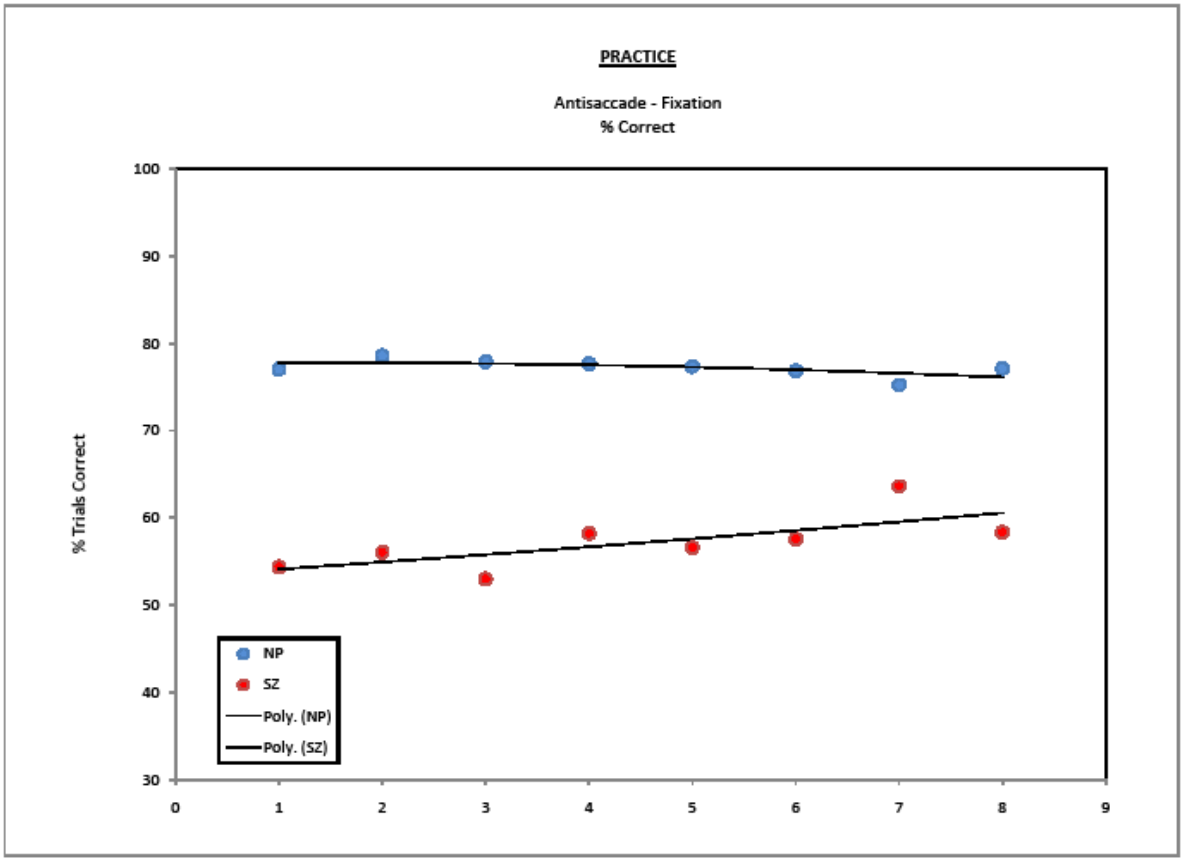


Figure 4.20 Practice Sessions: Antisaccade Percent Correct Curve

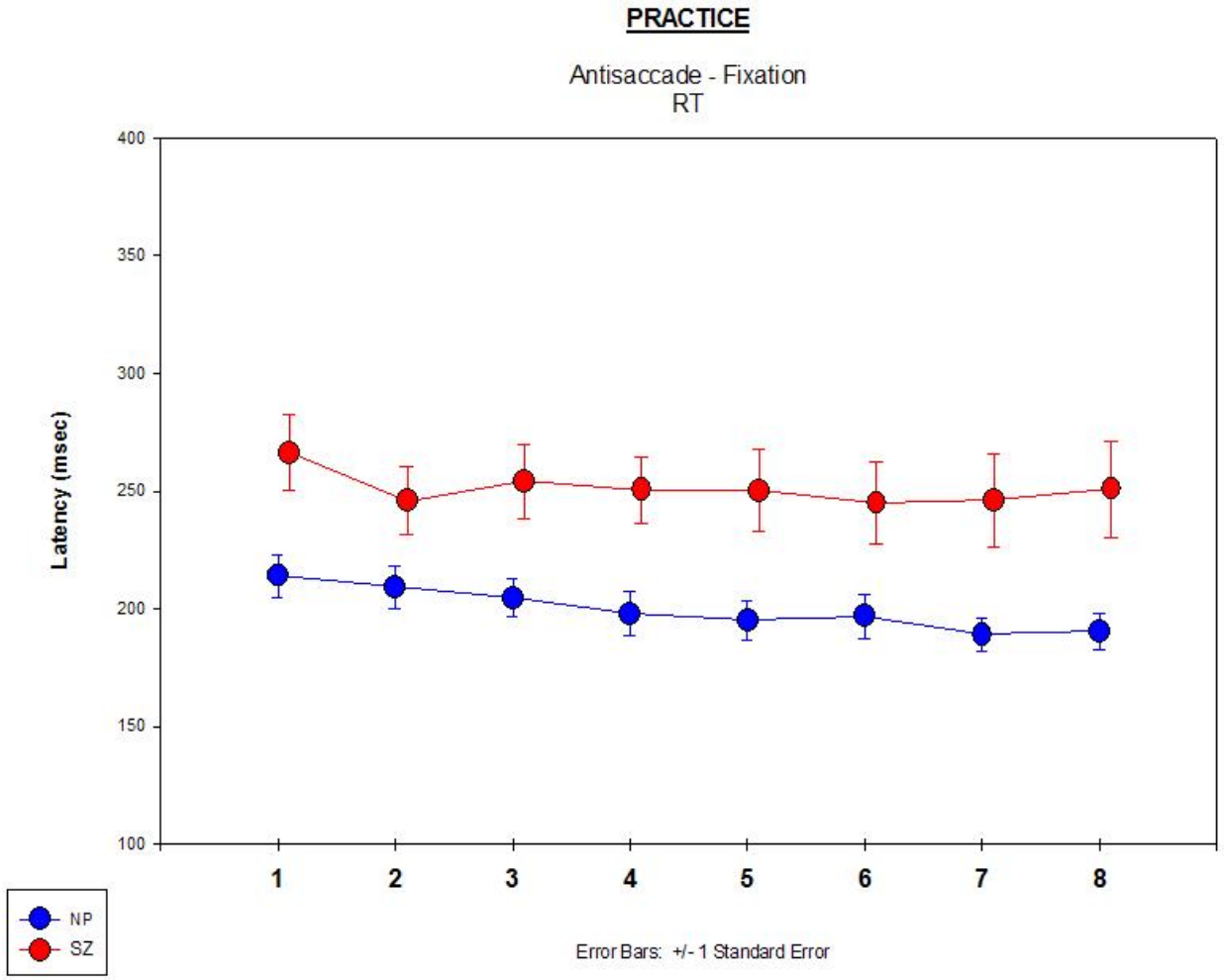


Figure 4.21 Practice Sessions: Antisaccade Latency

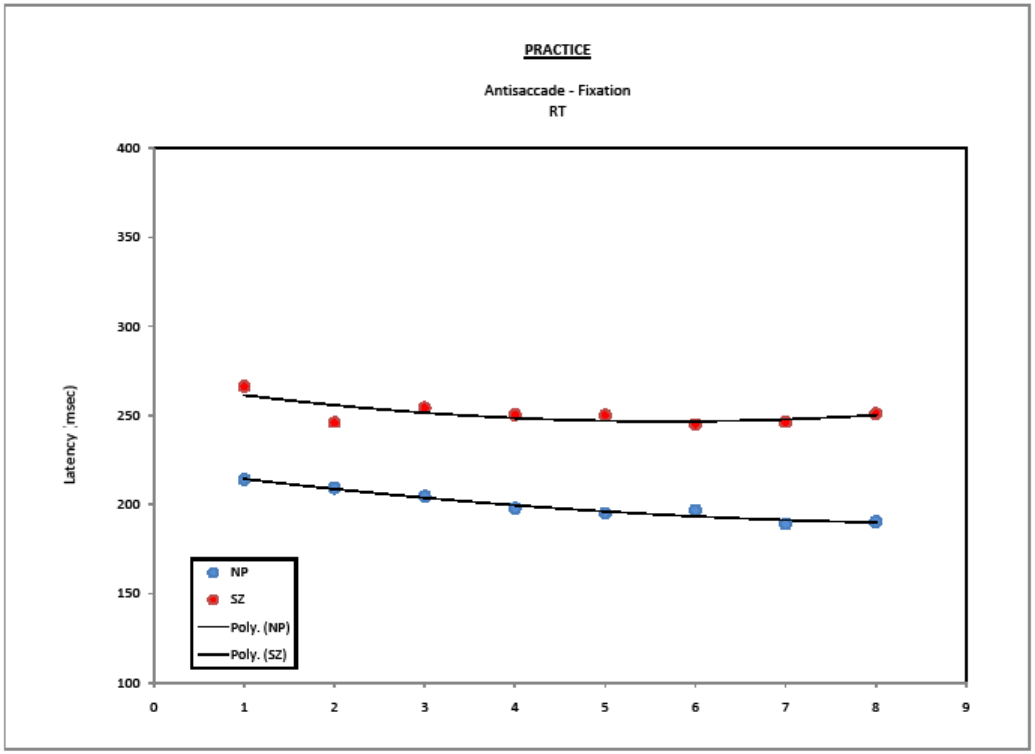


Figure 4.22 Practice Sessions: Antisaccade Latency Curve

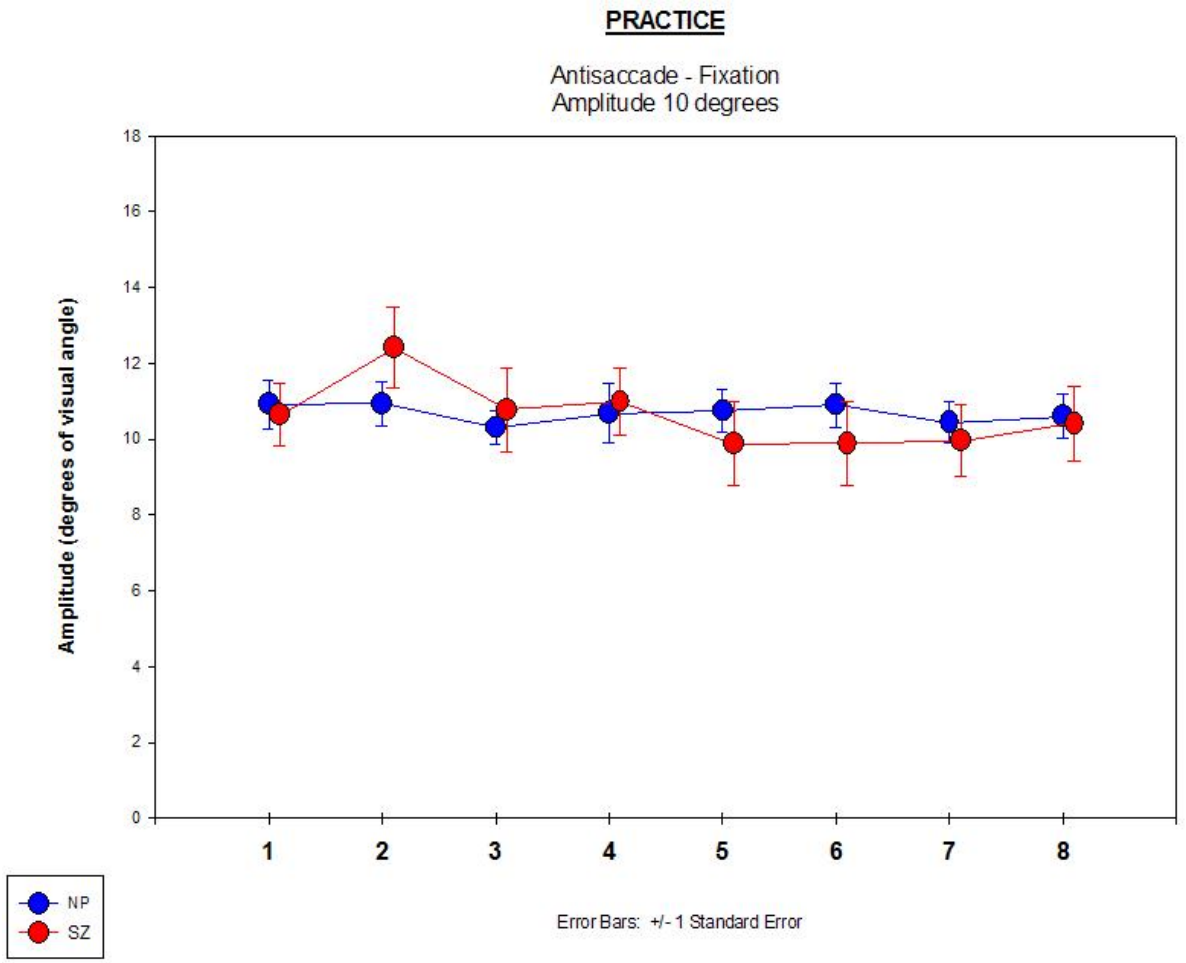


Figure 4.23 Practice Sessions: Antisaccade Accuracy: 10-Degree Eccentricity

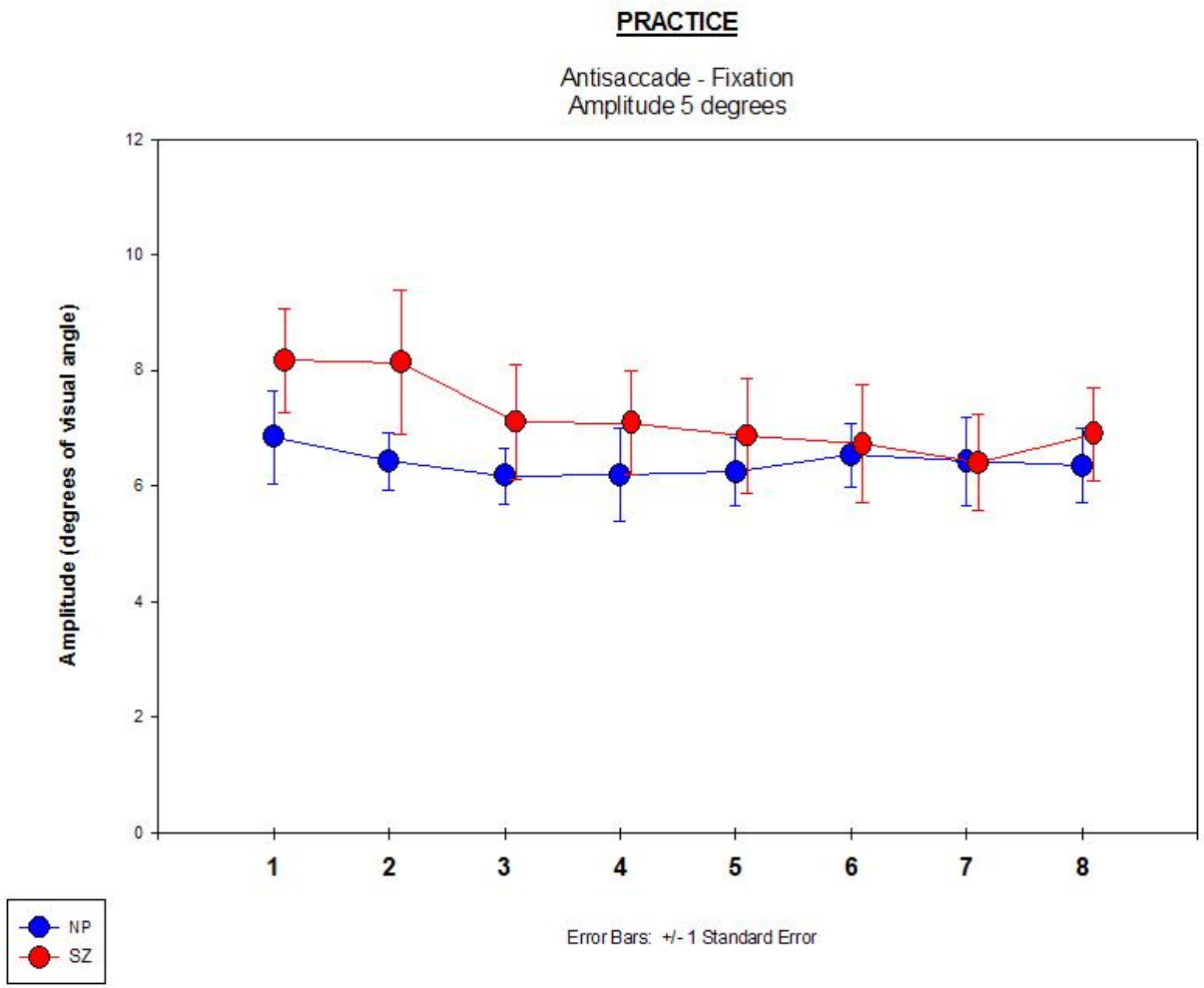


Figure 4.24 Practice Sessions: Antisaccade Accuracy: 5-Degree Eccentricity

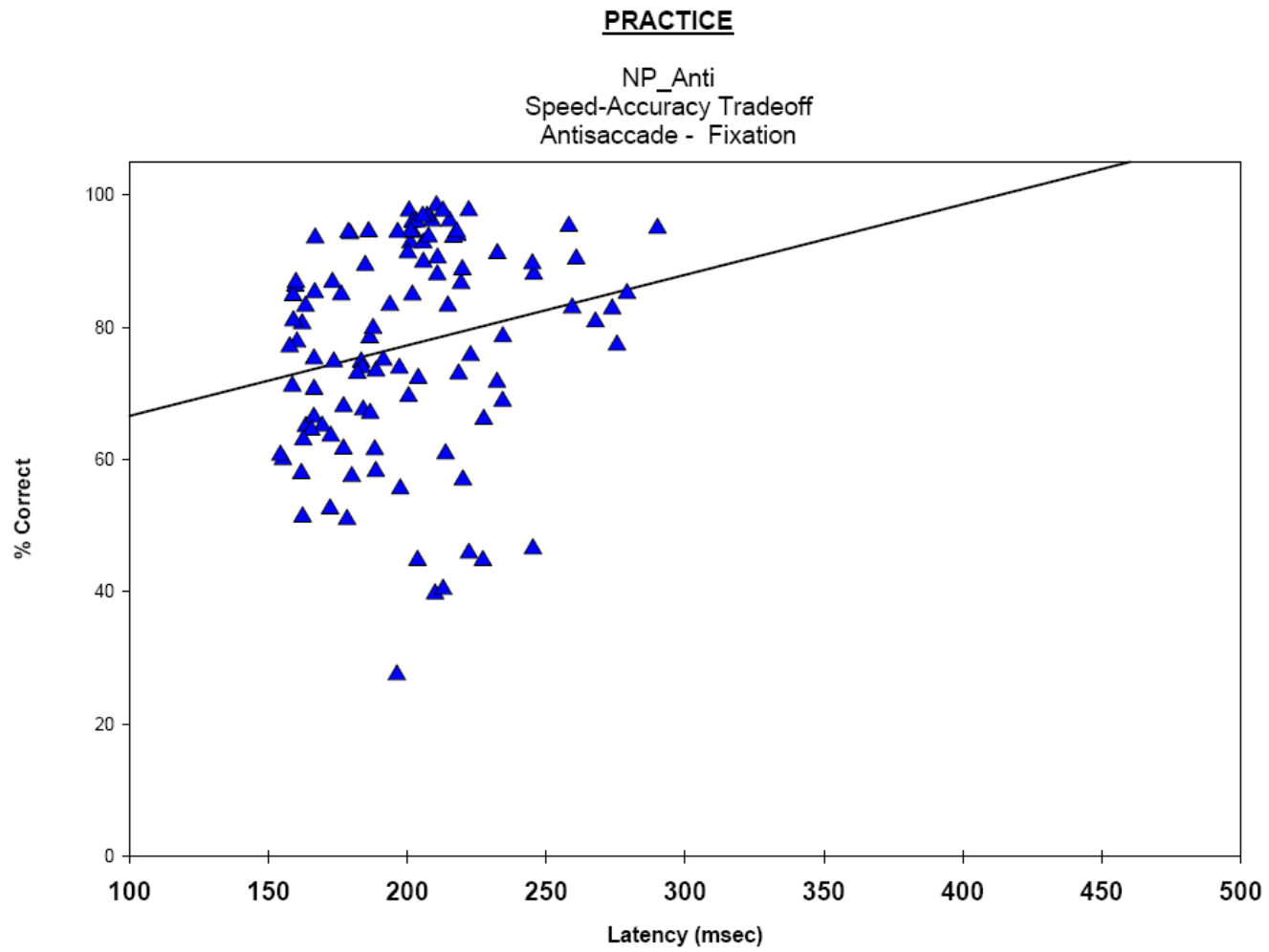


Figure 4.25 Practice Sessions: Antisaccade Speed-Accuracy Tradeoff for Normal Antisaccade Practice Group

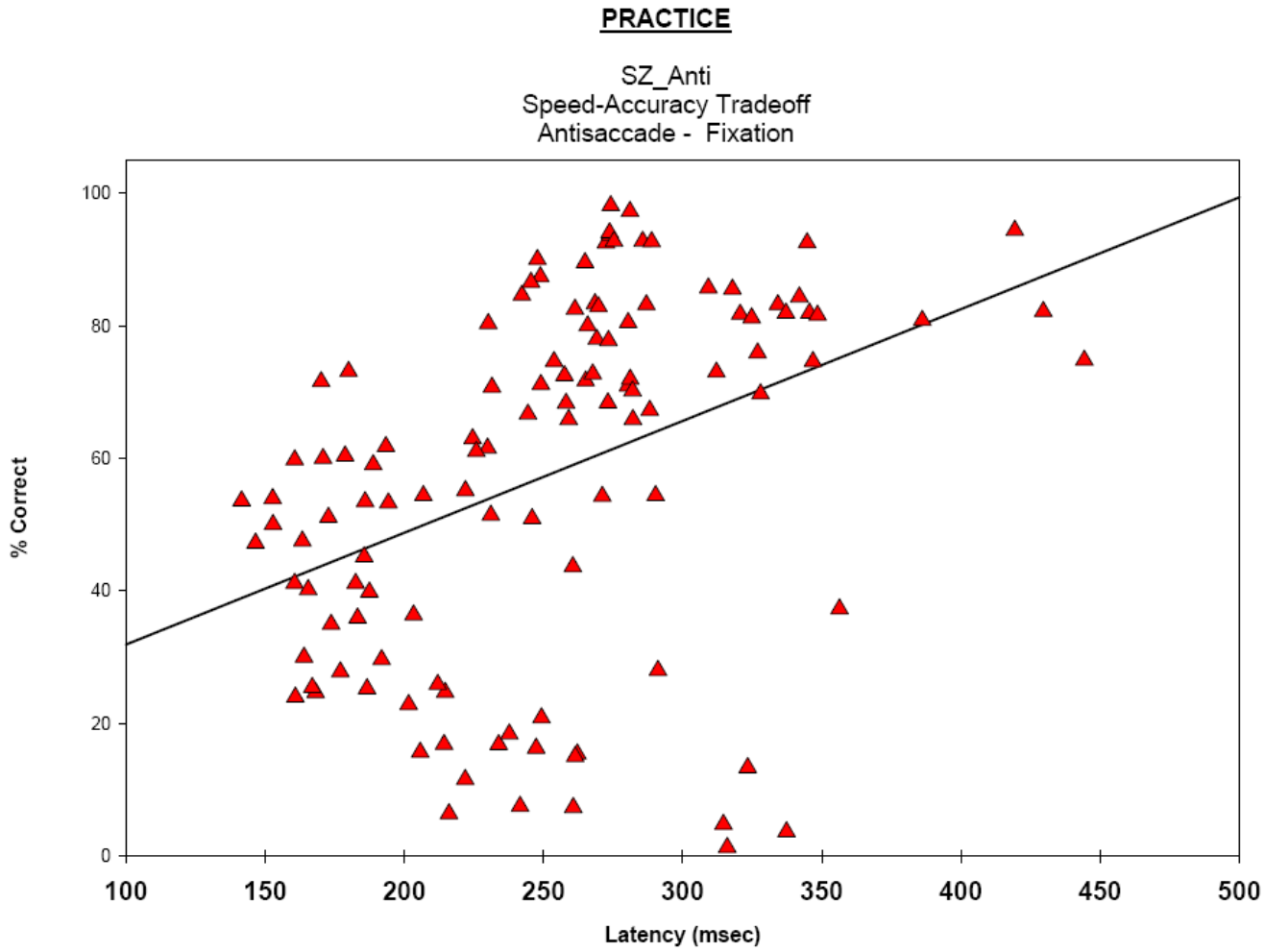


Figure 4.26 Practice Sessions: Antisaccade Speed-Accuracy Tradeoff for Schizophrenia Antisaccade Practice Group

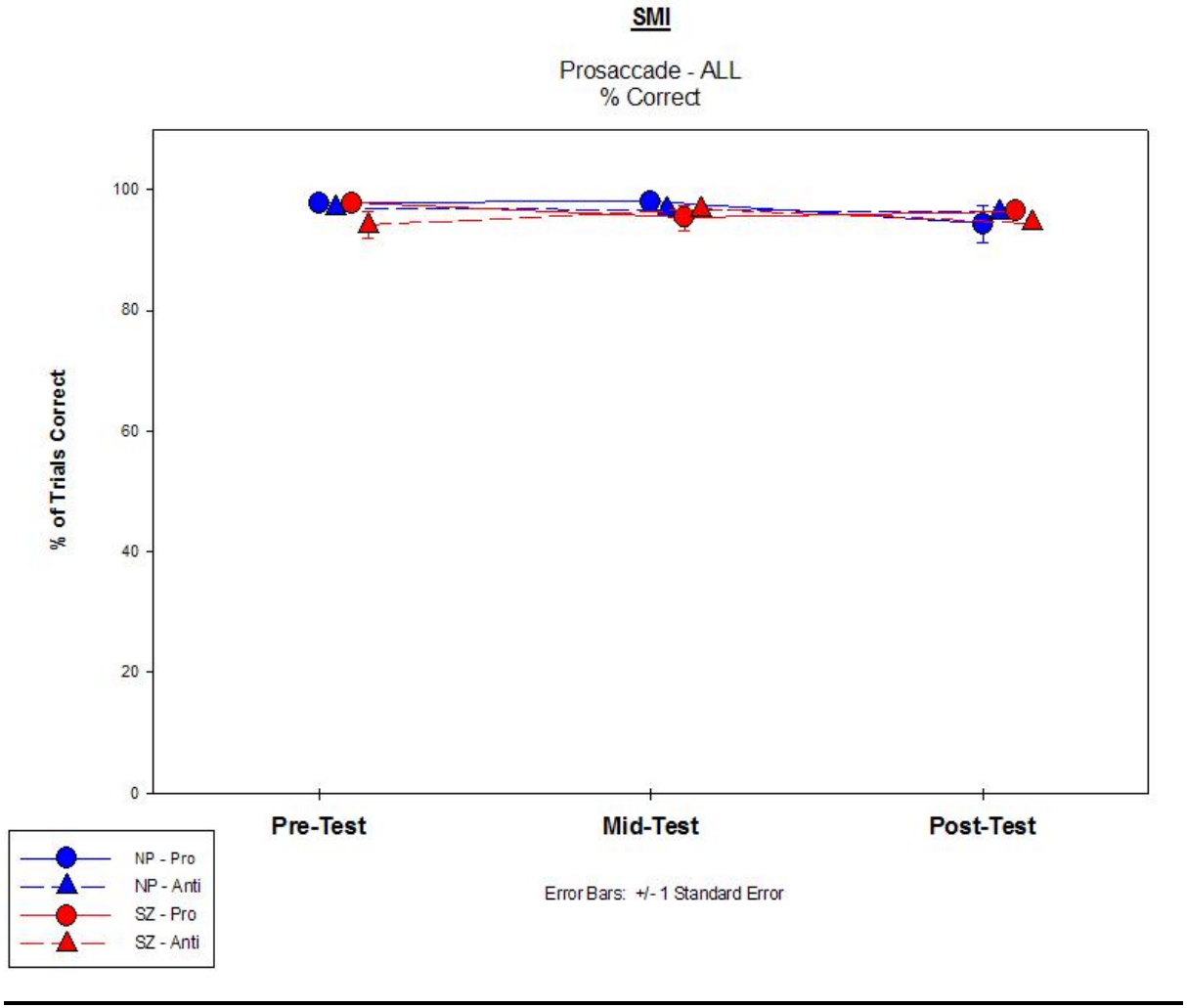


Figure 4.27 **Scanning Sessions: All Prosaccades Percent Correct**

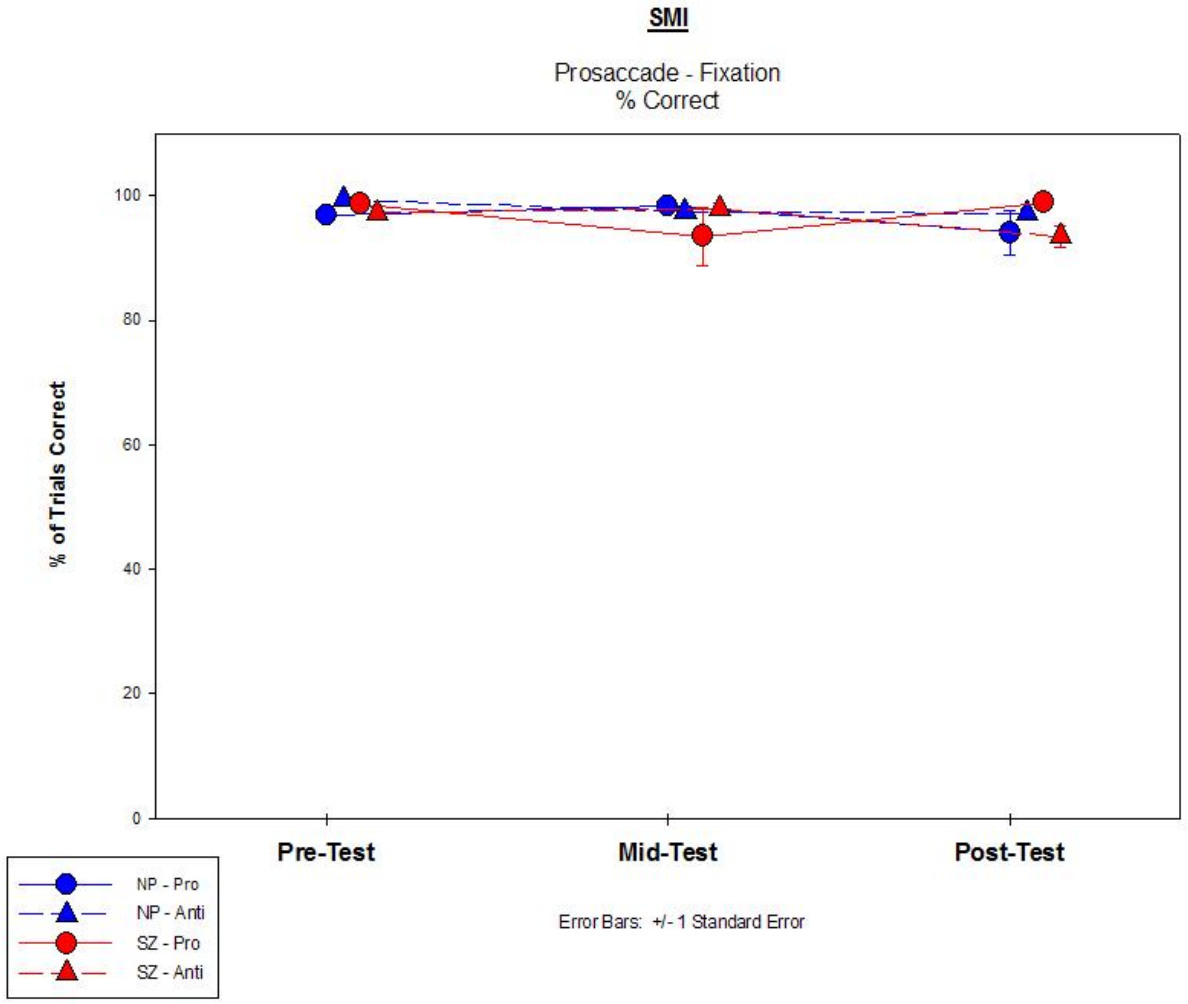


Figure 4.28 **Scanning Sessions: Prosaccade Percent Correct from Prosaccade/Fixation Paradigm**

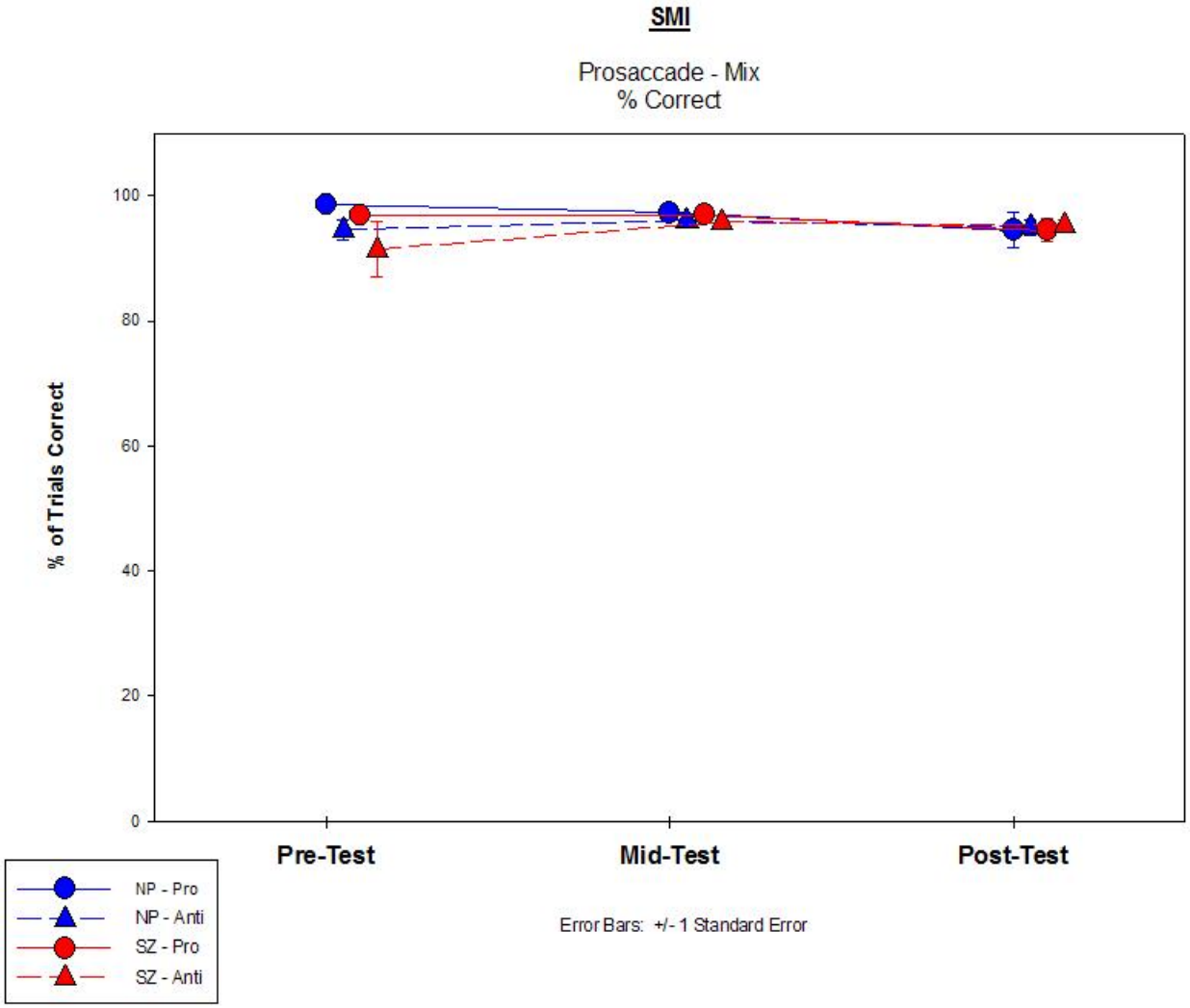


Figure 4.29 Scanning Sessions: Prosaccade Percent Correct from Antisaccade/Prosaccade Paradigm

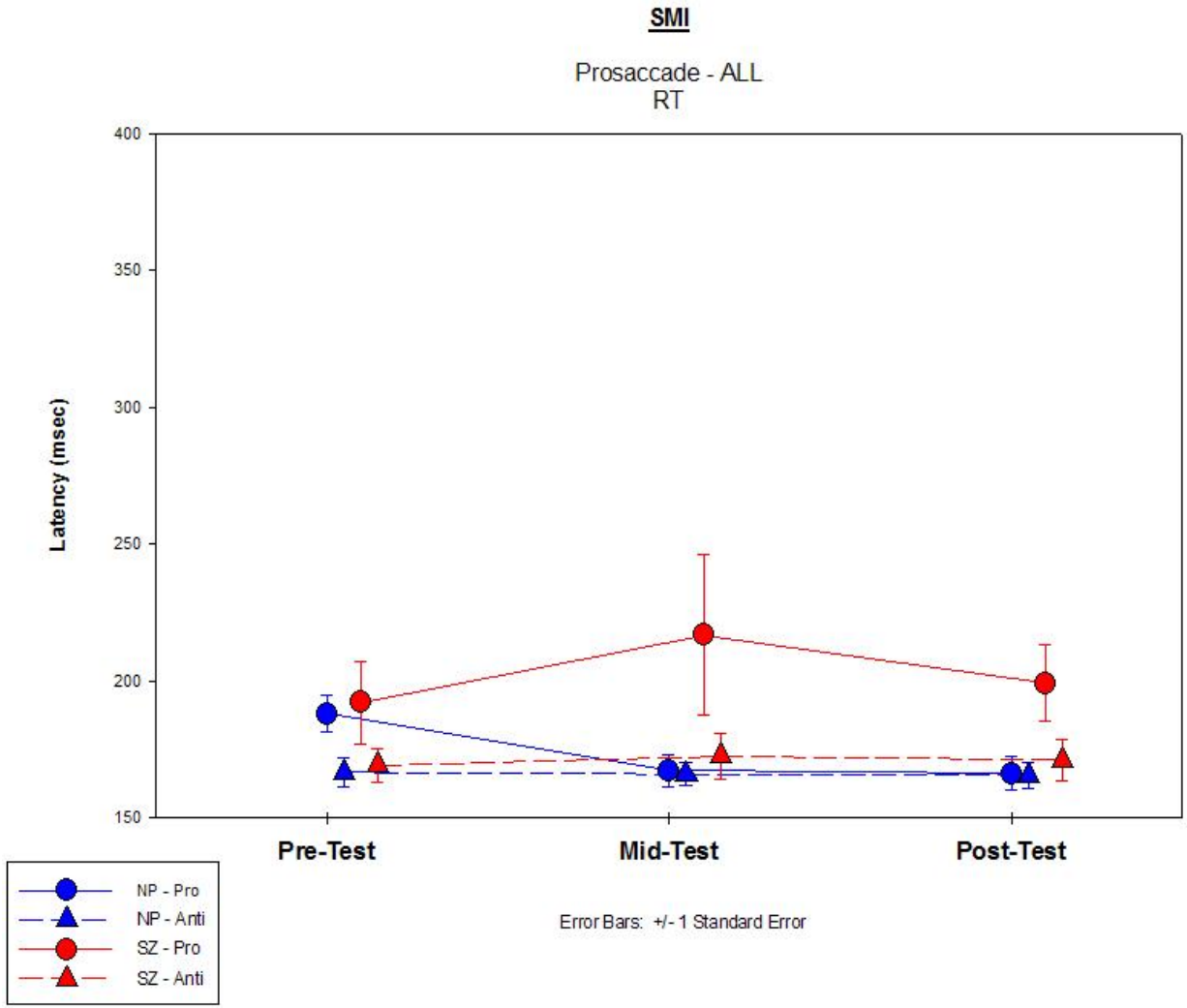


Figure 4.30 Scanning Sessions: All Prosaccades Latency

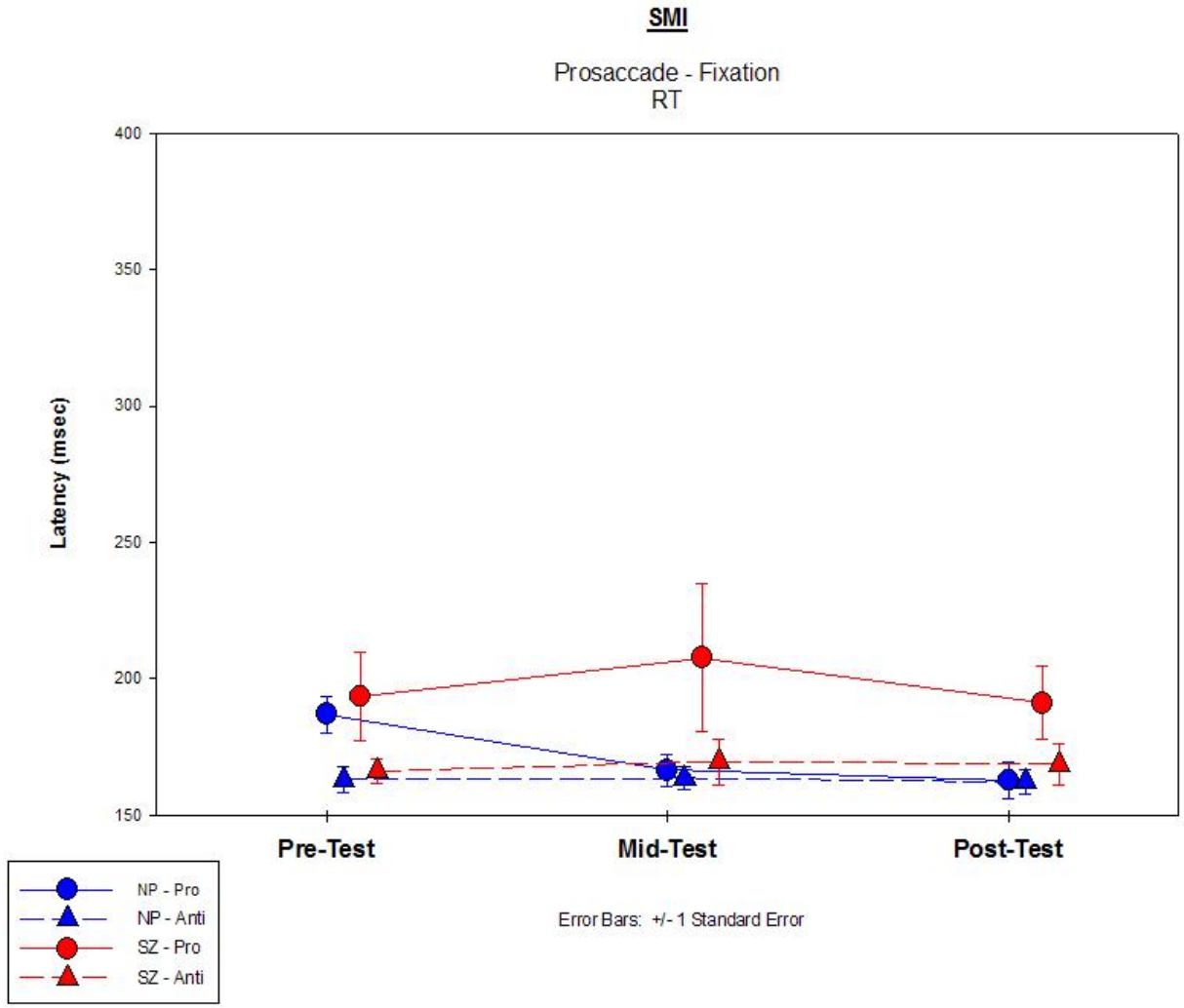


Figure 4.31 Scanning Sessions: Prosaccades Latency from Prosaccade/Fixation Paradigm

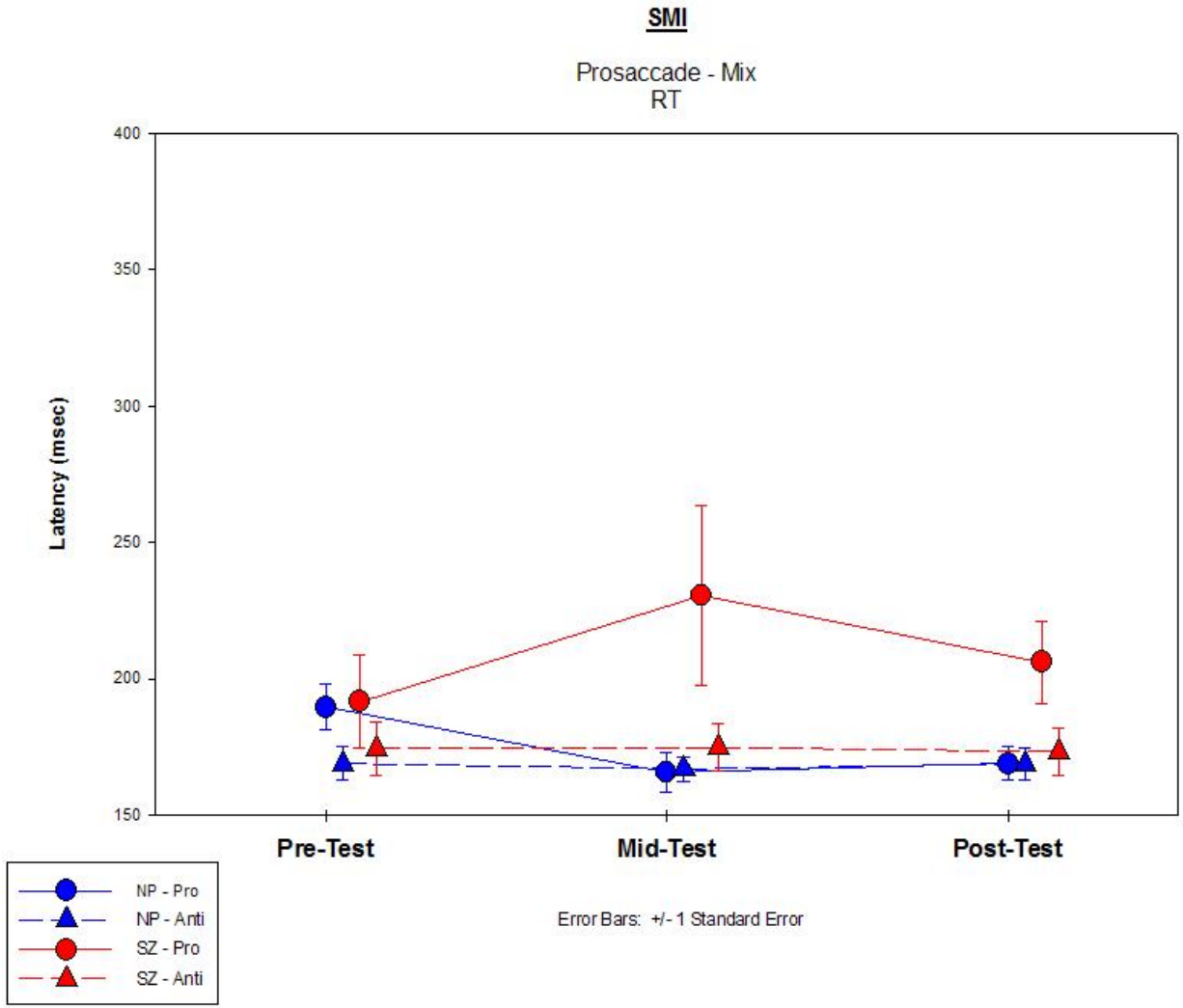


Figure 4.32 Scanning Sessions: Prosaccades Latency from Antisaccade/Prosaccade Paradigm

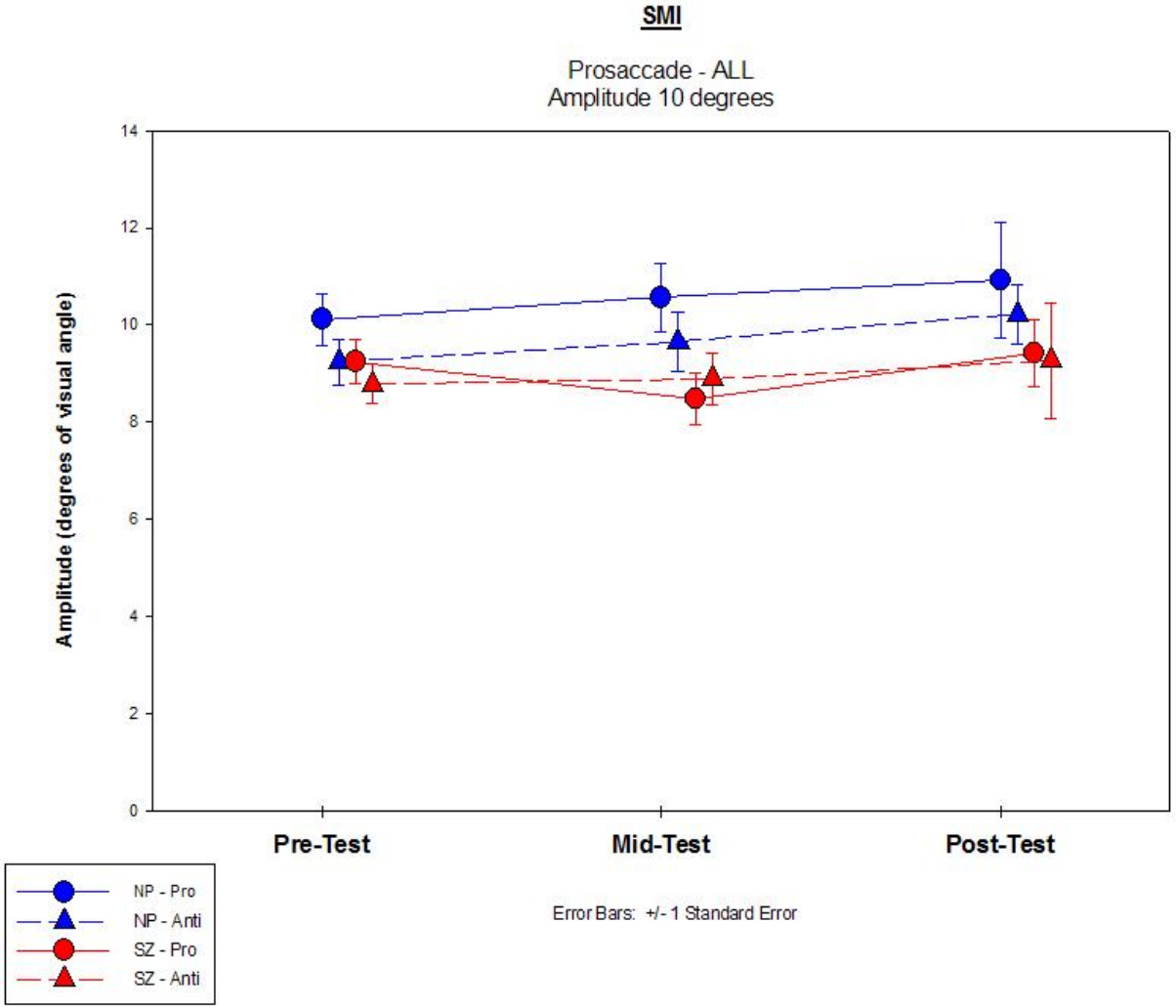


Figure 4.33 Scanning Sessions: All Prosaccades Accuracy for 10-Degree Eccentricity

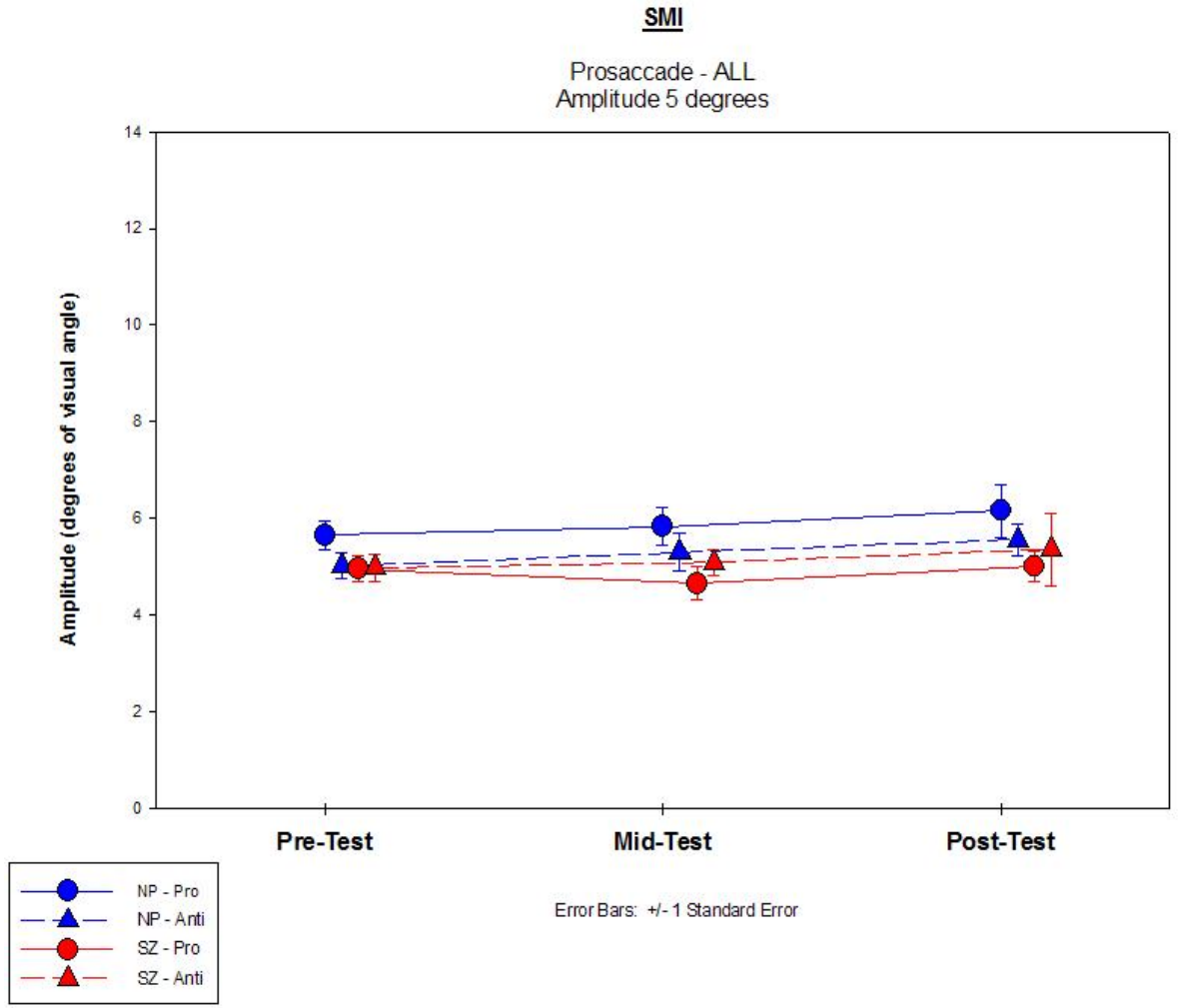


Figure 4.34 Scanning Sessions: All Prosaccades Accuracy for 5-Degree Eccentricity

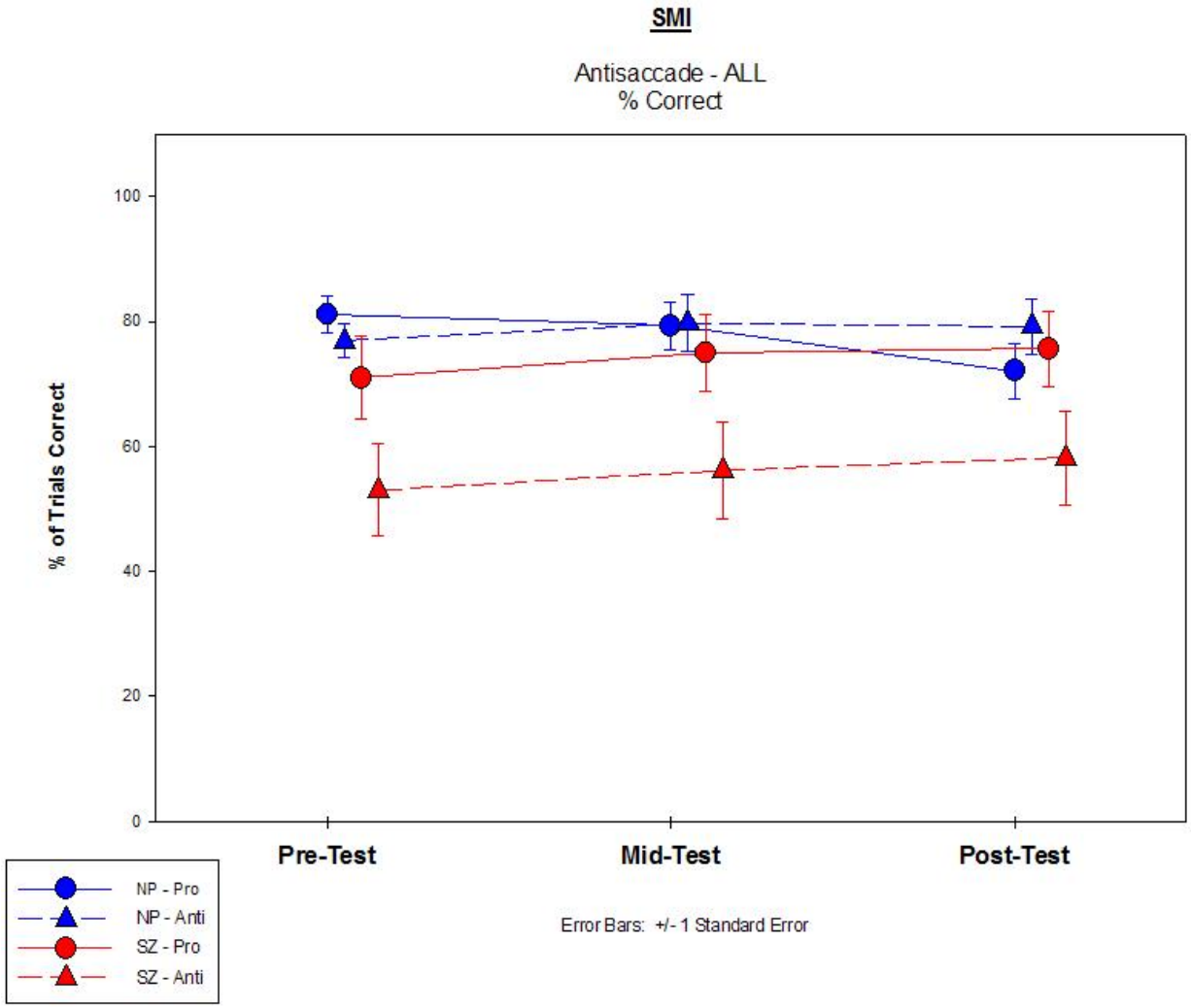


Figure 4.35 Scanning Sessions: All Antisaccade Percent Correct

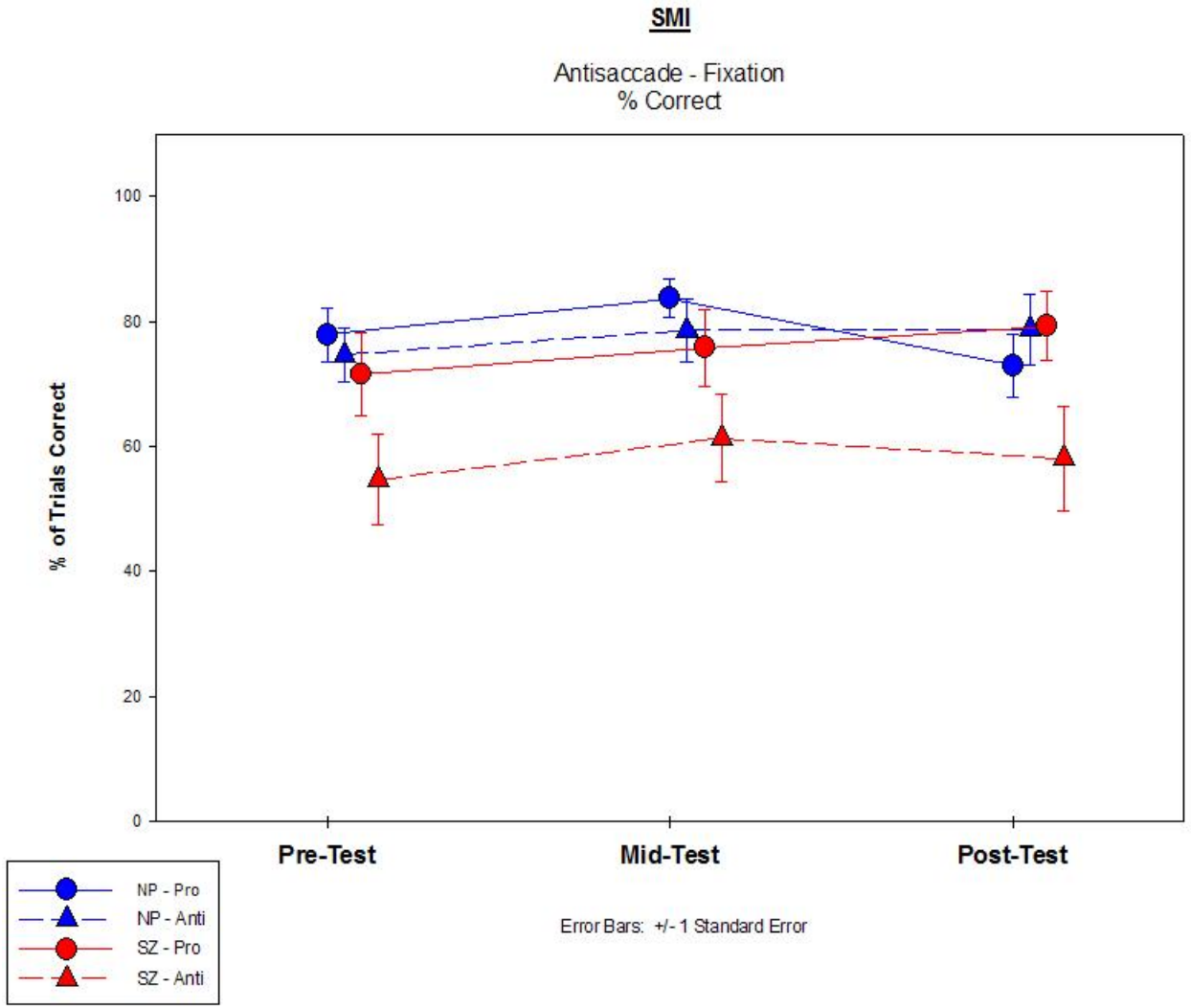


Figure 4.36 **Scanning Sessions: Antisaccade Percent Correct from Antisaccade/Fixation Paradigm**

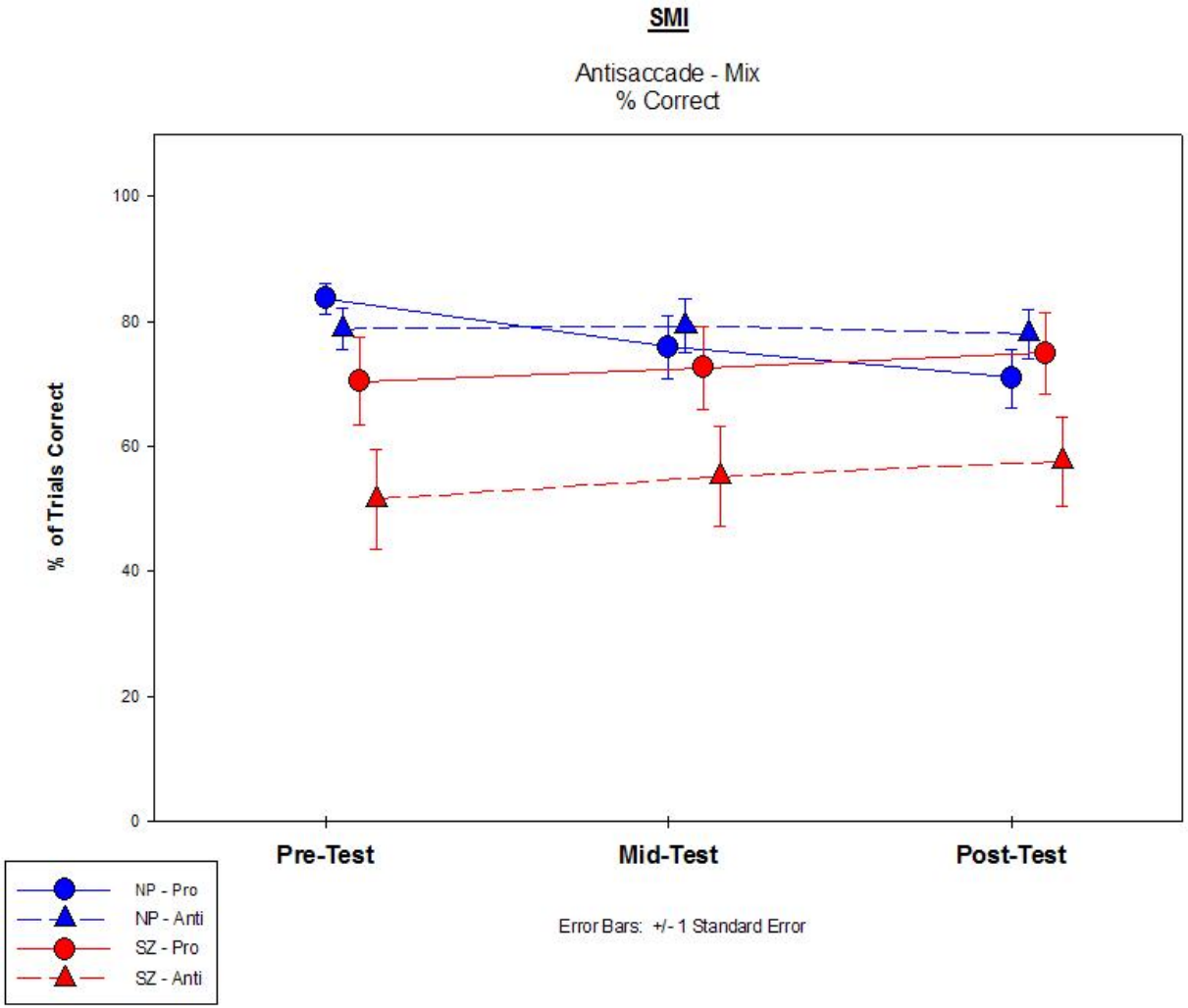


Figure 4.37 Scanning Sessions: Antisaccade Percent Correct from Antisaccade/Prosaccade Paradigm

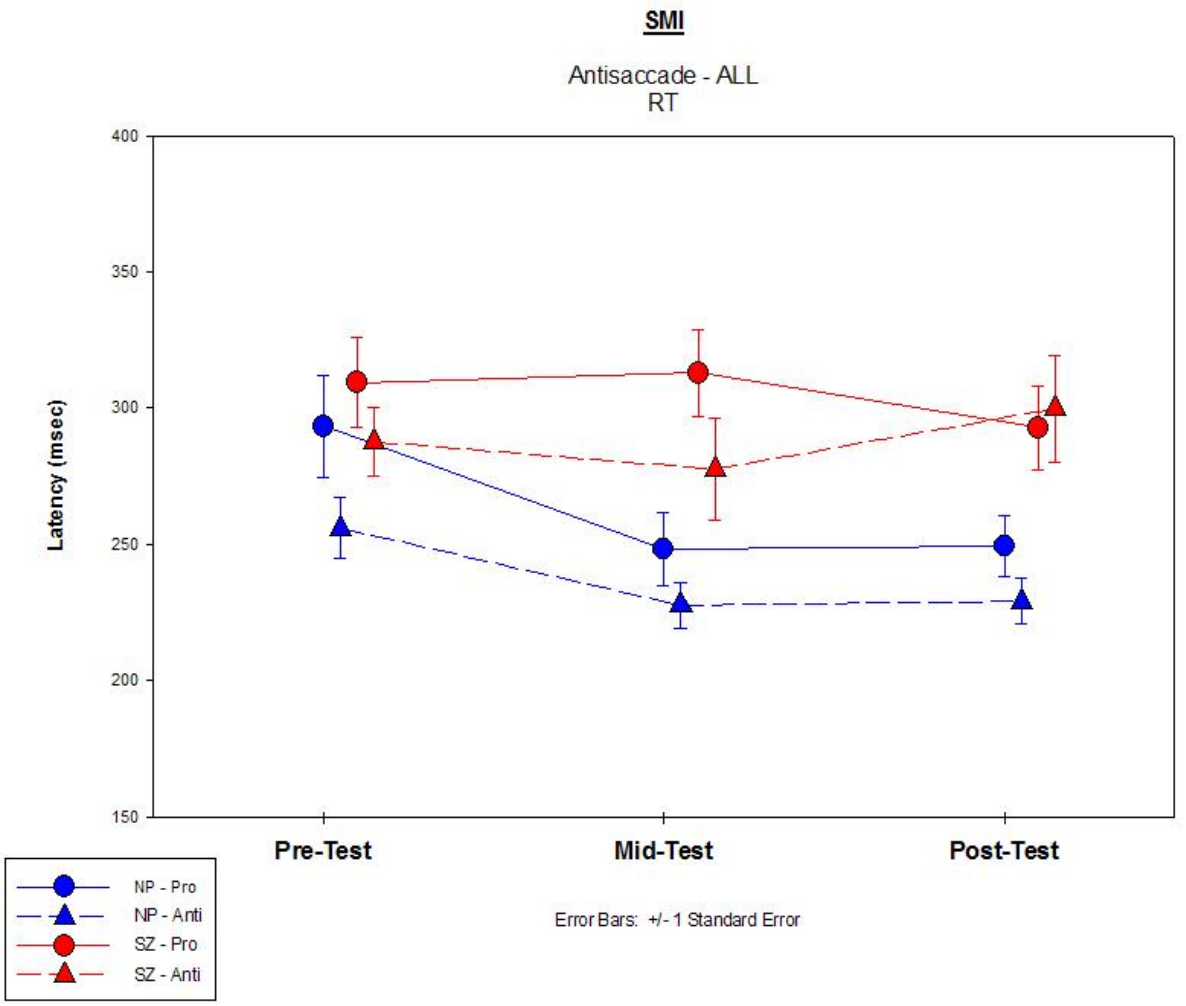


Figure 4.38 Scanning Sessions: All Antisaccades Latency

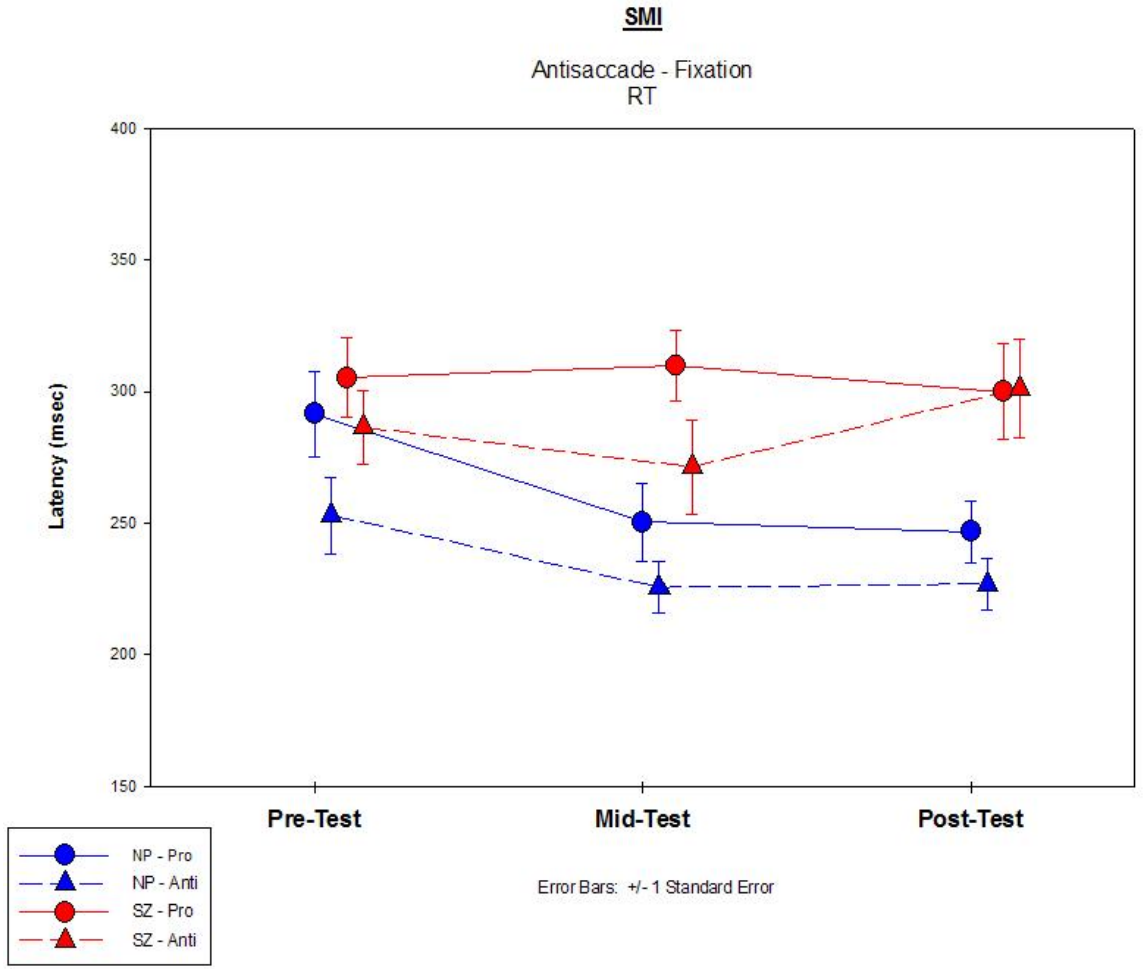


Figure 4.39 Scanning Sessions: Antisaccade Latency from Antisaccade/Fixation Paradigm

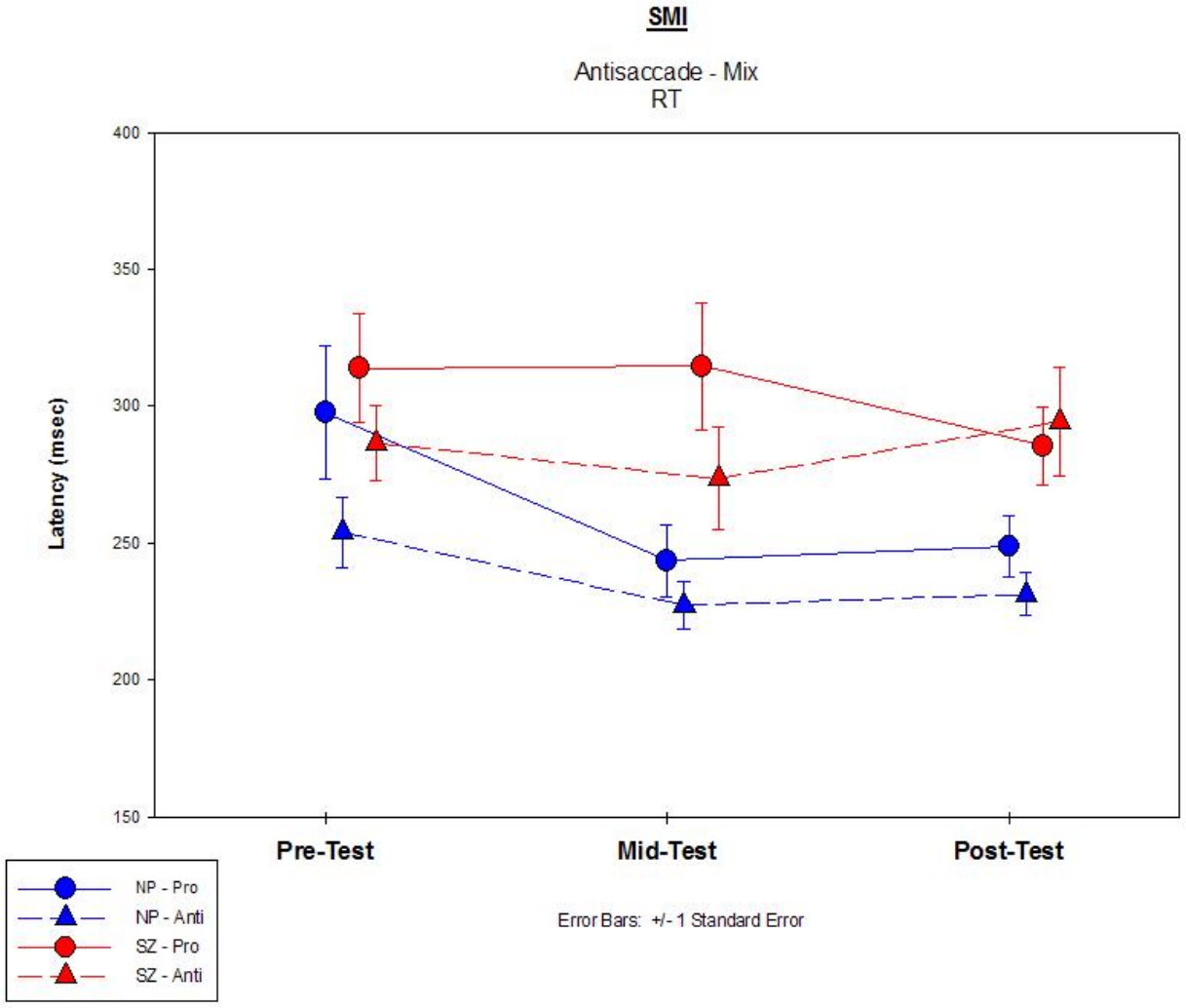


Figure 4.40 **Scanning Sessions: Antisaccade Latency from Antisaccade/Prosaccade Paradigm**

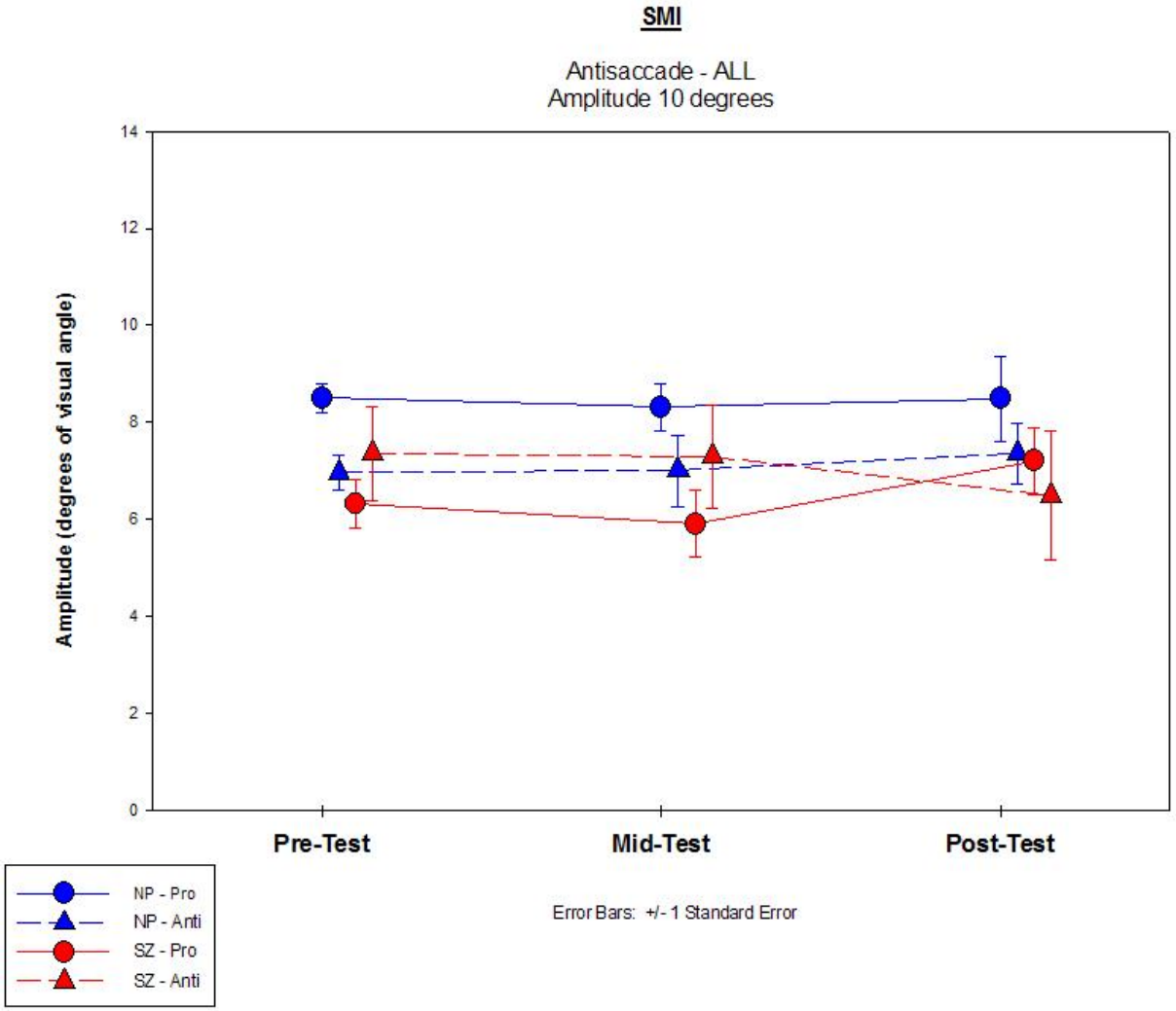


Figure 4.41 **Scanning Sessions: All Antisaccades Accuracy for 10-Degree Eccentricity**

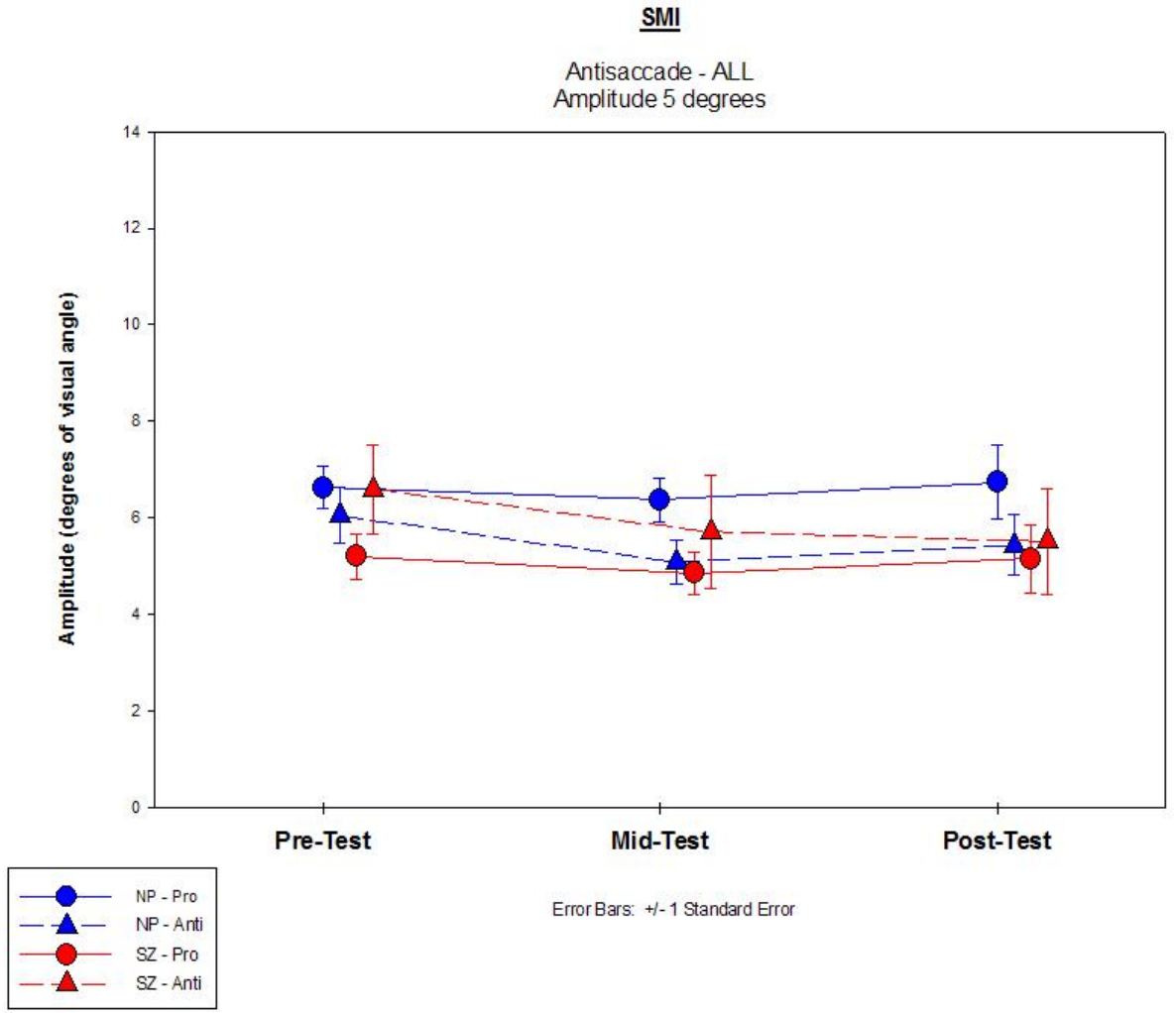


Figure 4.42 Scanning Sessions: All Antisaccades Accuracy for 5-Degree Eccentricity

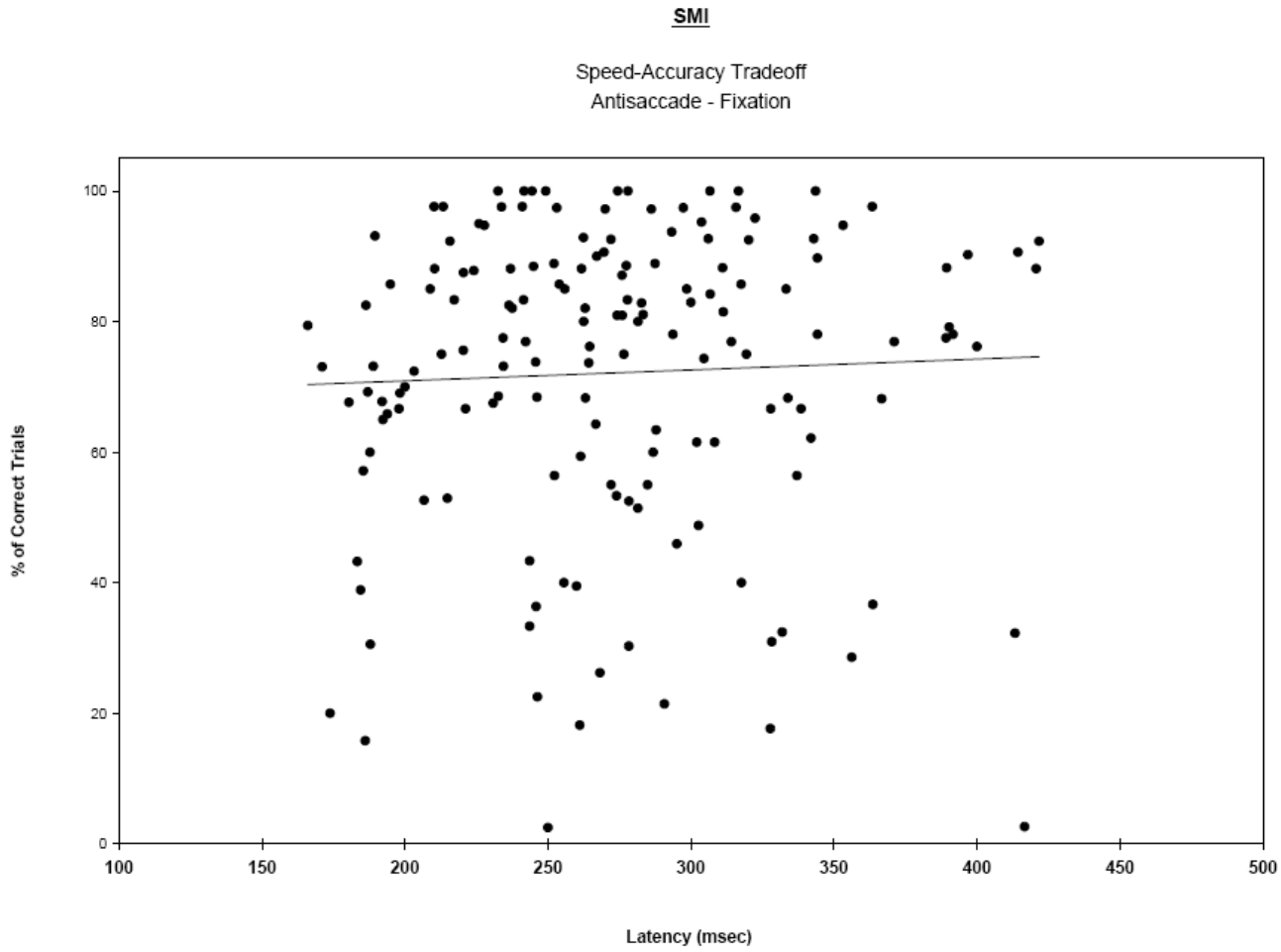


Figure 4.43 Scanning Sessions: Speed-Accuracy Tradeoff from Antisaccade-Fixation Paradigm 1
Shown for all subjects at pre-, mid-, and post-test combined.

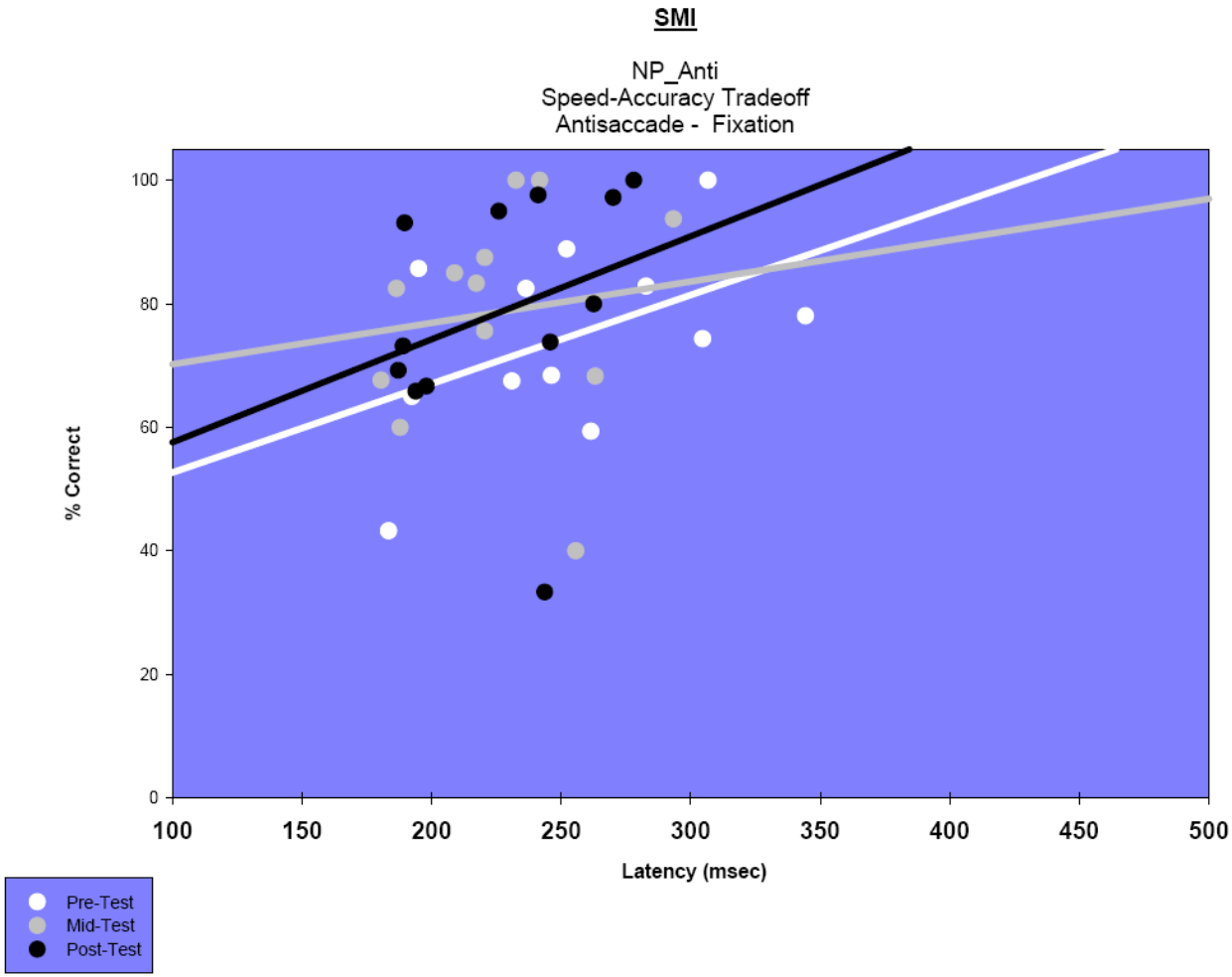


Figure 4.44 Scanning Sessions: Speed-Accuracy Tradeoff from Antisaccade-Fixation Paradigm 2
Shown for normal antisaccade practice group.

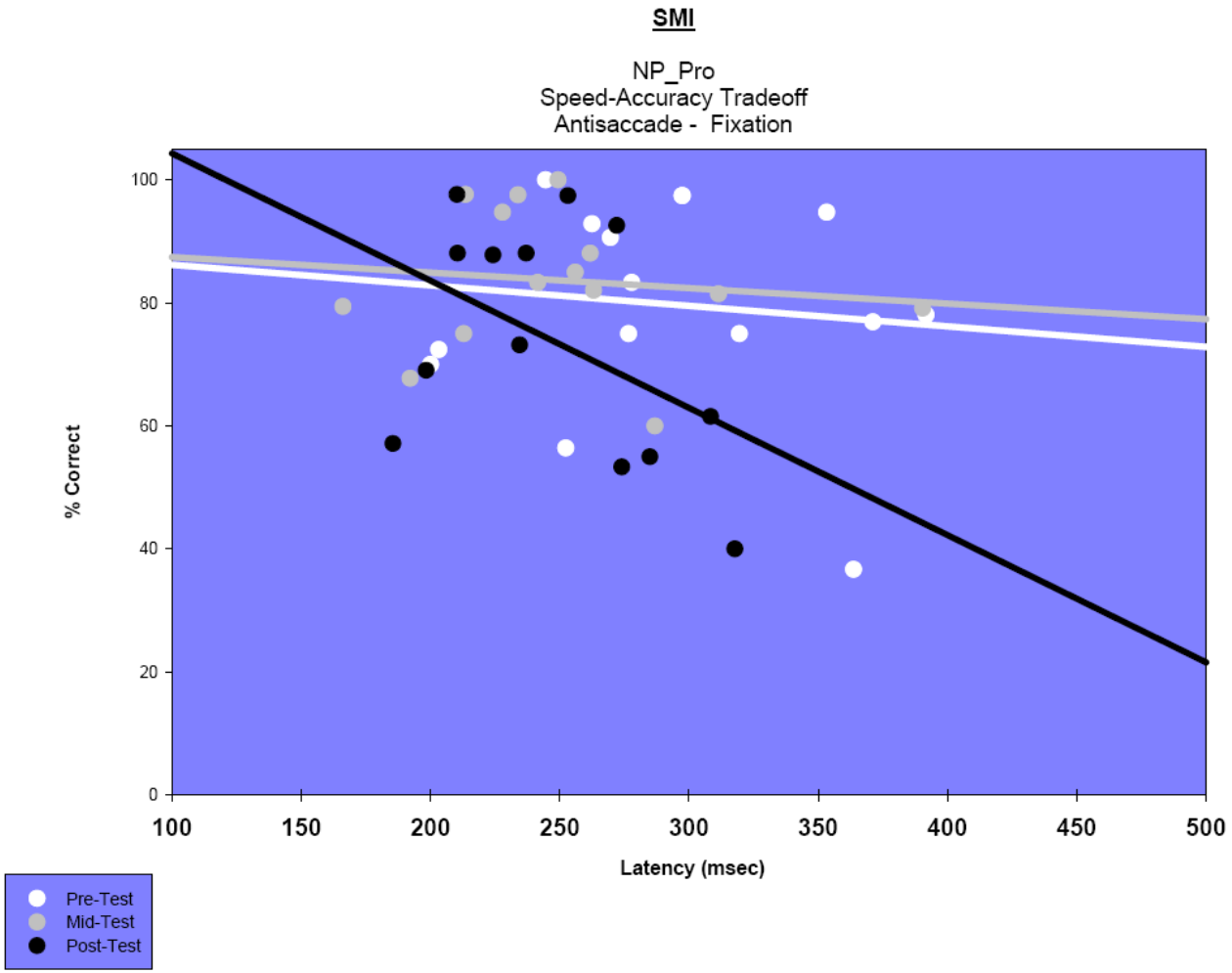


Figure 4.45 Scanning Sessions: Speed-Accuracy Tradeoff from Antisaccade-Fixation Paradigm 3
Shown for normal prosaccade practice group.

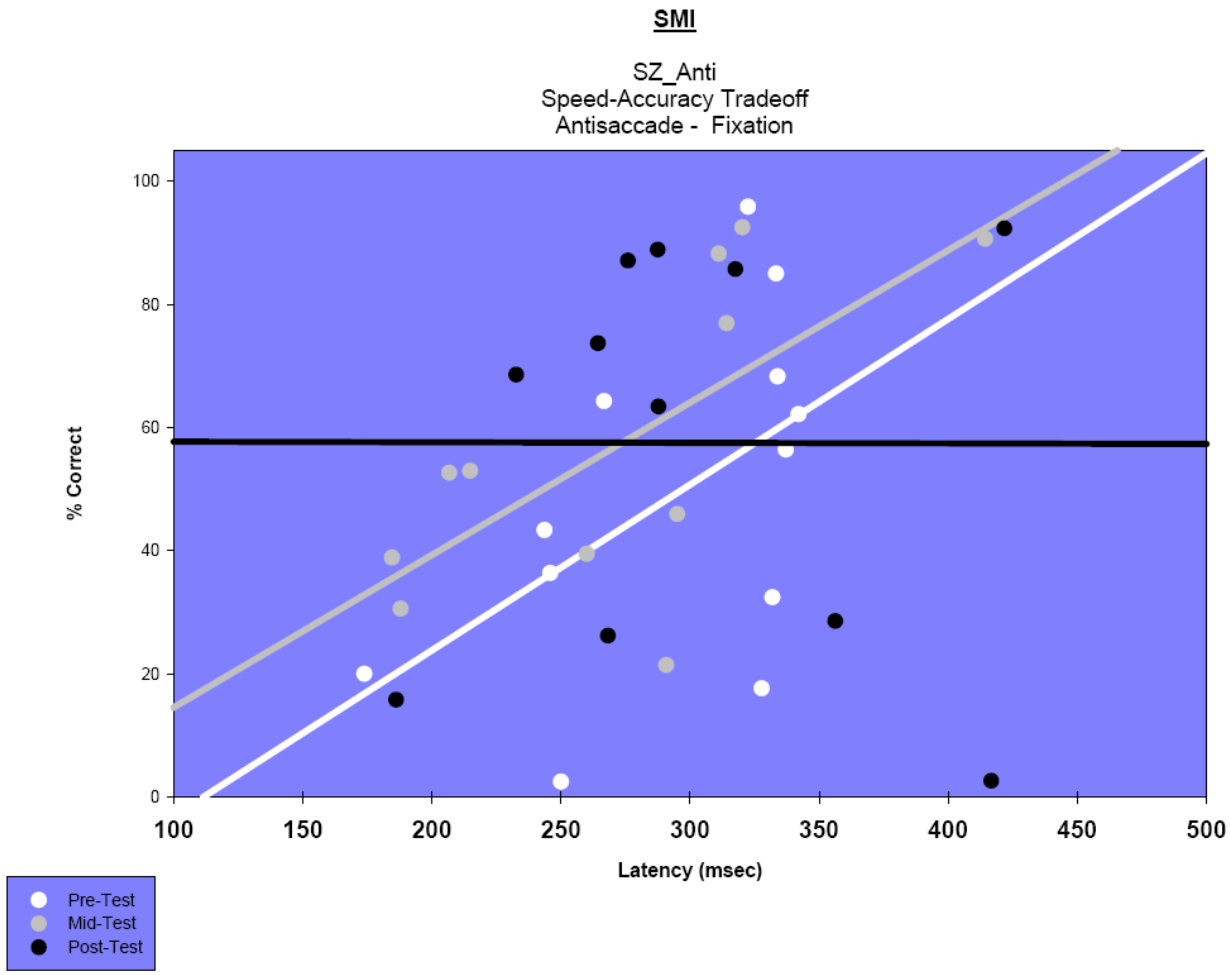


Figure 4.46 Scanning Sessions: Speed-Accuracy Tradeoff from Antisaccade-Fixation Paradigm 4
Shown for schizophrenia antisaccade practice group.

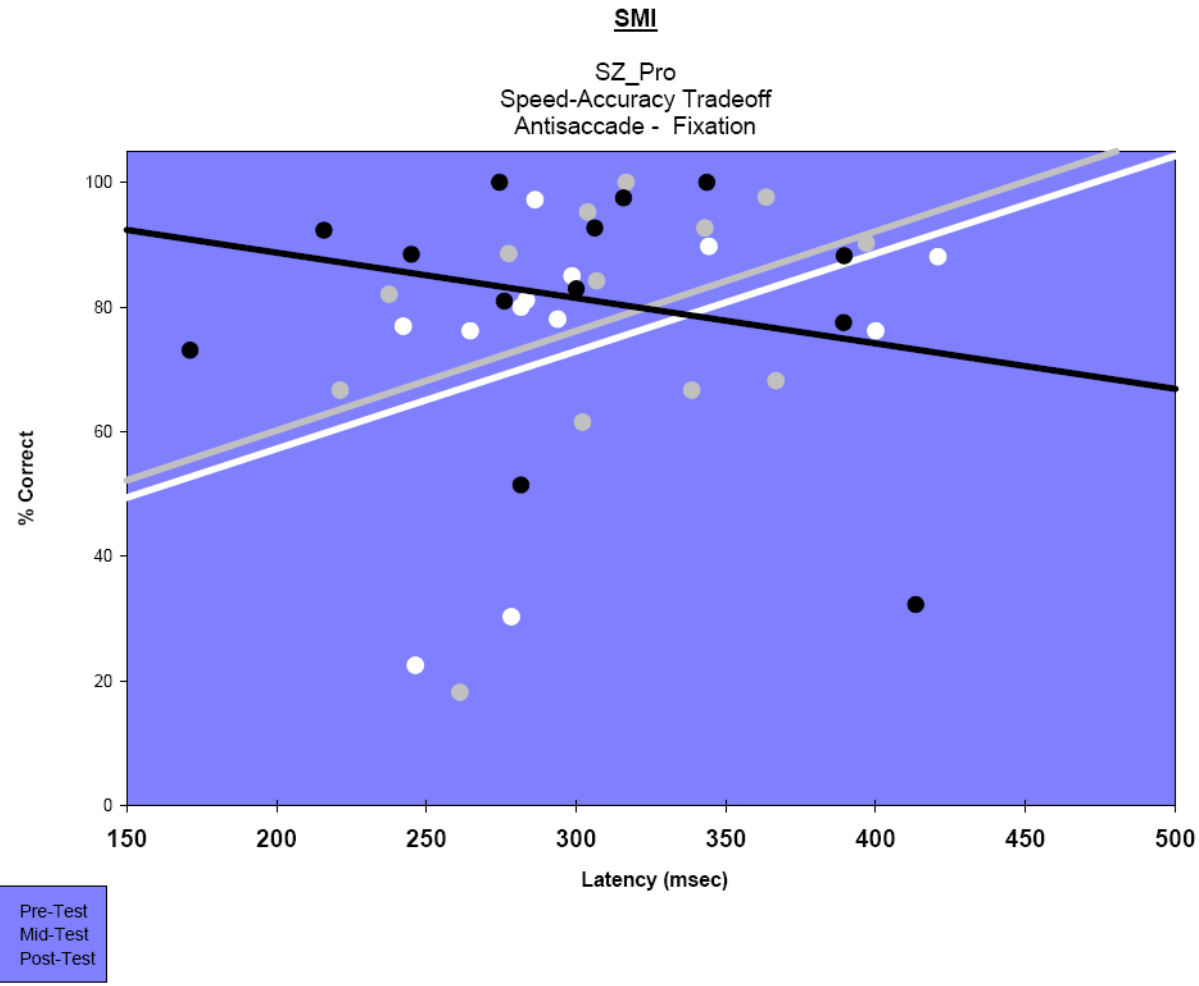


Figure 4.47 Scanning Sessions: Speed-Accuracy Tradeoff from Antisaccade-Fixation Paradigm 5
Shown for schizophrenia prosaccade practice group.

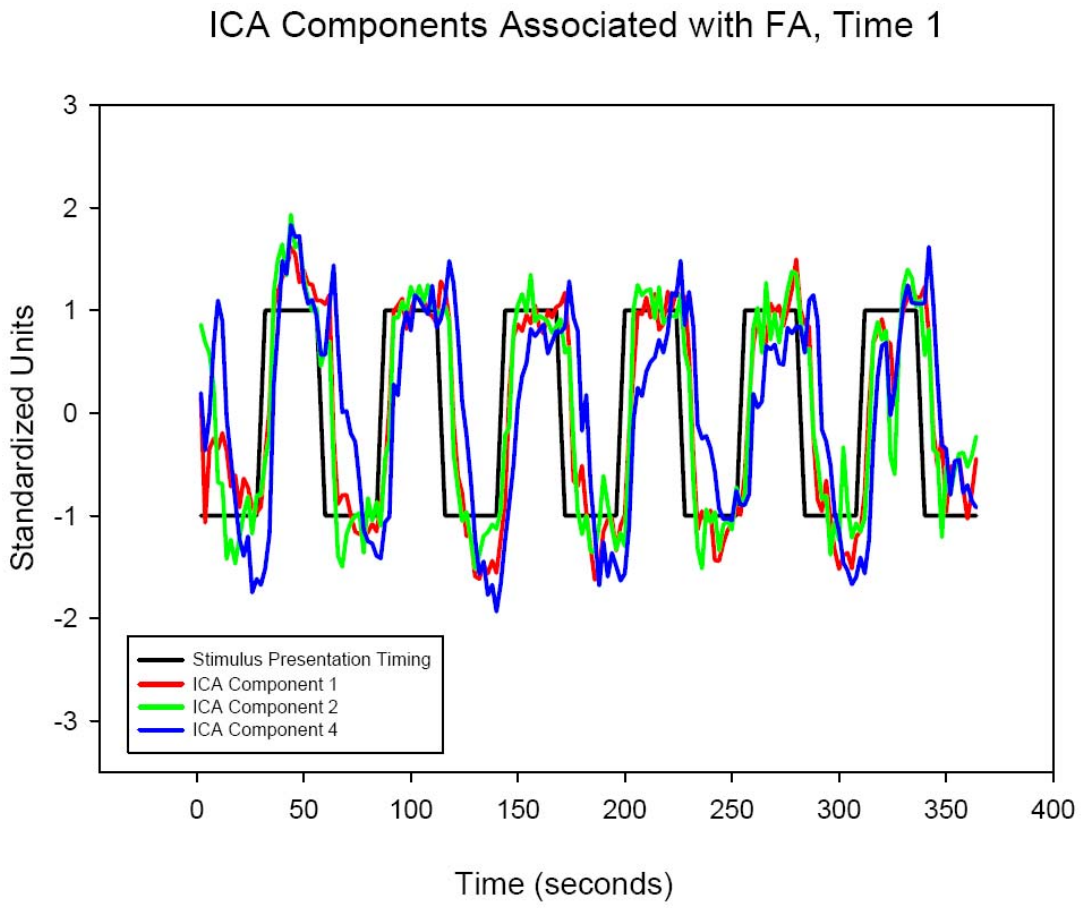


Figure 4.48 ICA Components most Associated with Pre-Test Session. Plots of stimulus presentation (black line) and task-related ICA components across the length of a run. For the stimulus presentation plot, -1 represents the baseline condition, +1 represents the experimental condition. Component 1 is shown in red, component 2 is shown in green, component 4 is shown in blue.

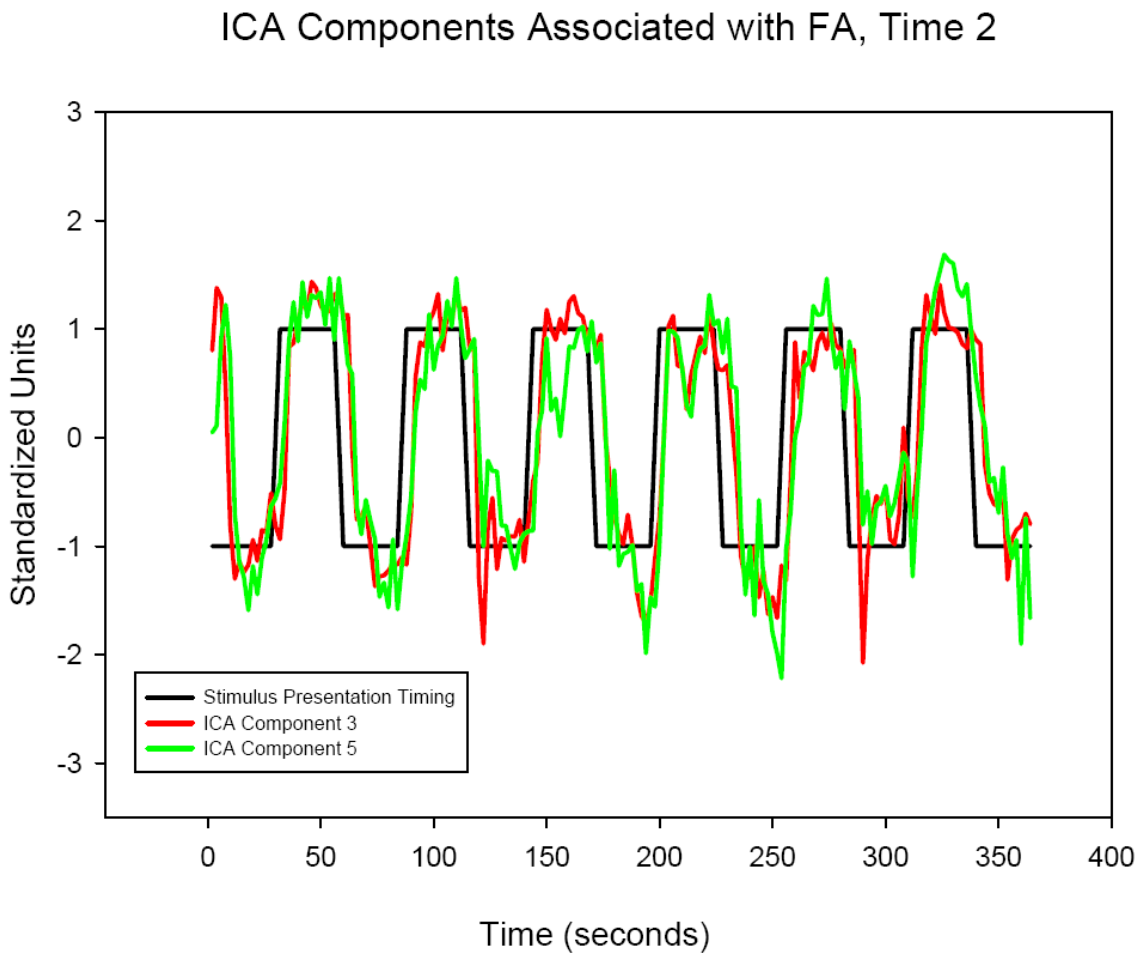
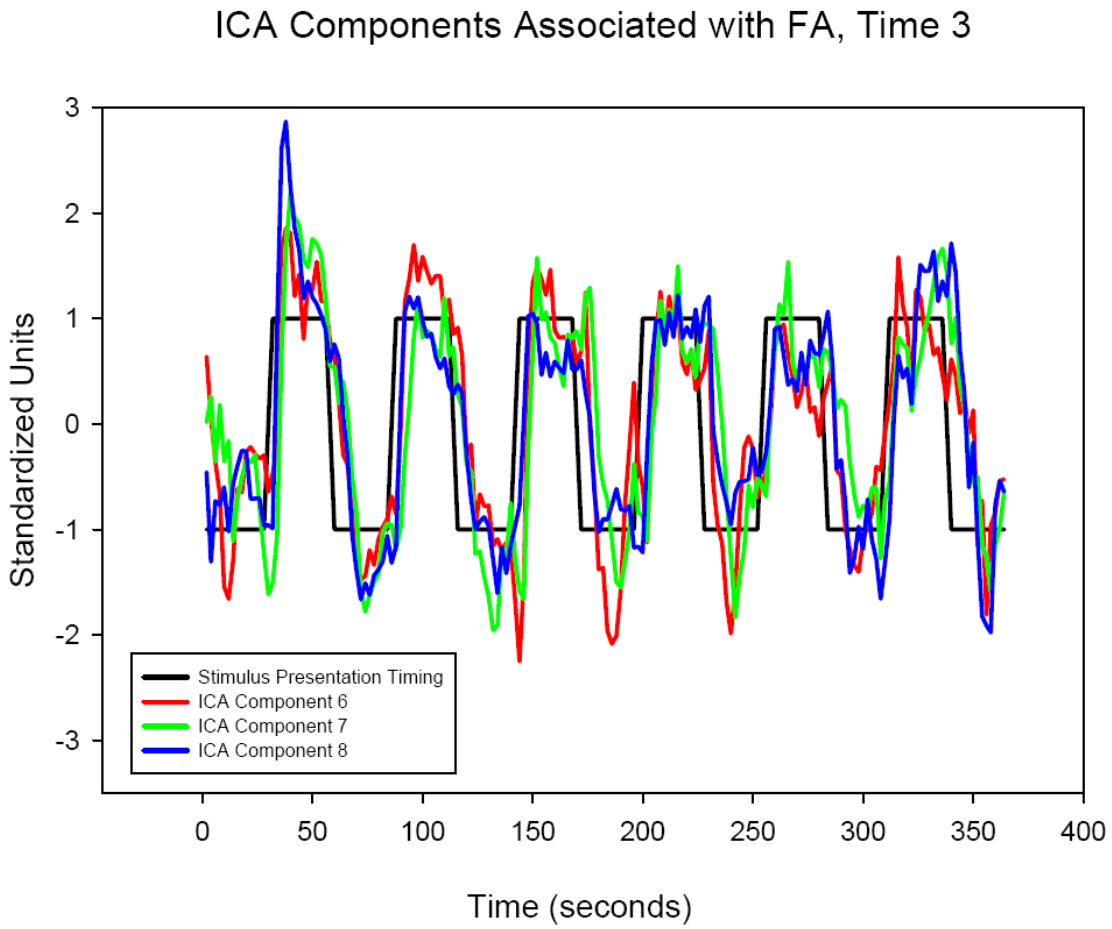


Figure 4.49 ICA Components most Associated with Mid-Test Session. Plots of stimulus presentation (black line) and task-related ICA components across the length of a run. For the stimulus presentation plot, -1 represents the baseline condition, +1 represents the experimental condition. Component 3 is shown in red, component 5 is shown in green.



<u>Figure 4.50</u> ICA Components most Associated with Post-Test Session. Plots of stimulus presentation (black line) and task-related ICA components across the length of a run. For the stimulus presentation plot, -1 represents the baseline condition, +1 represents the experimental condition. Component 6 is shown in red, component 7 is shown in green, component 8 is shown in blue.

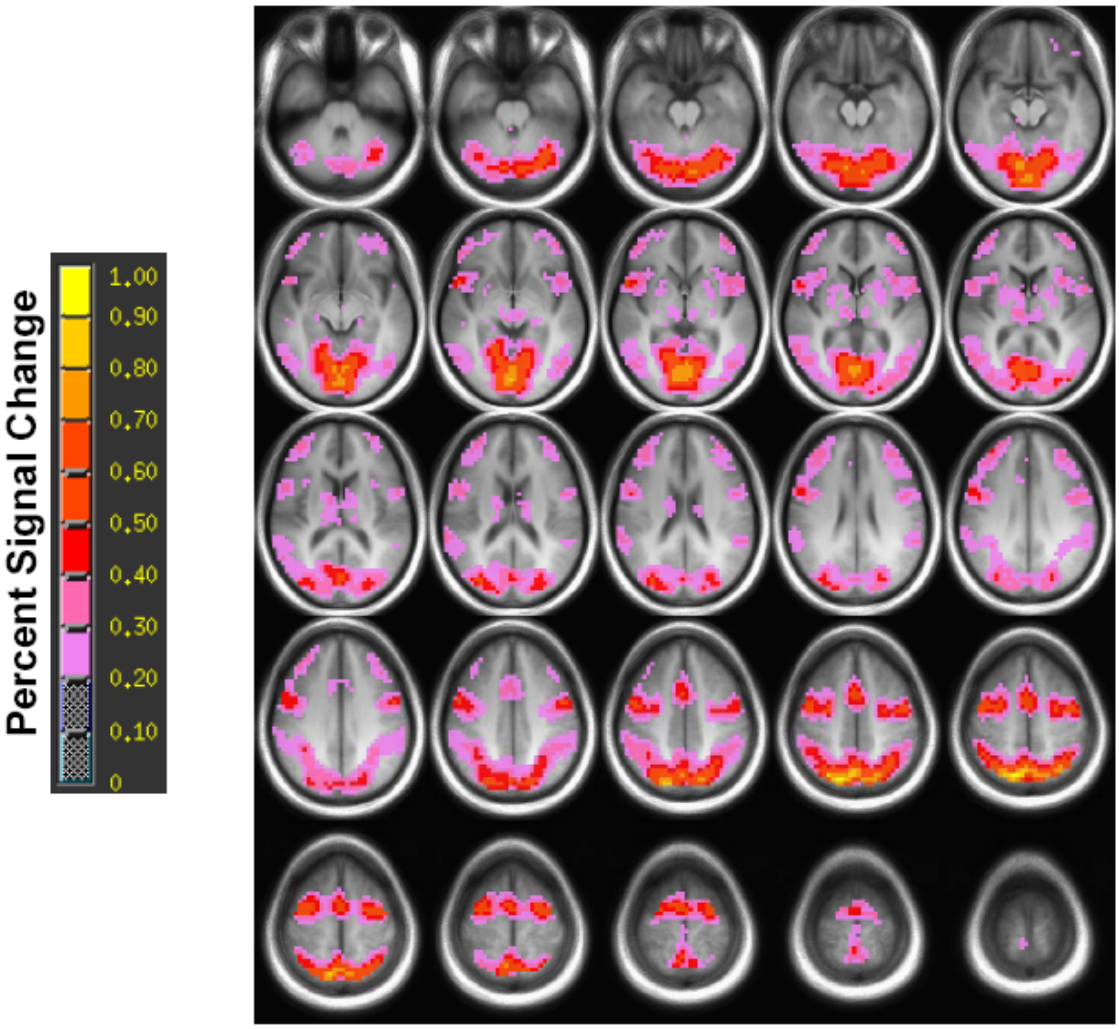


Figure 4.51 Antisaccade-related activity during Antisaccade/Fixation Paradigm across all timepoints. Functional magnetic resonance imaging results – whole-brain analysis results for all groups across all timepoints. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying regions with significant percent signal increase (indicated by the color scale) associated with antisaccade performance in all group across all timepoints. This one-sample *t* map was used to determine regions of interest. The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).

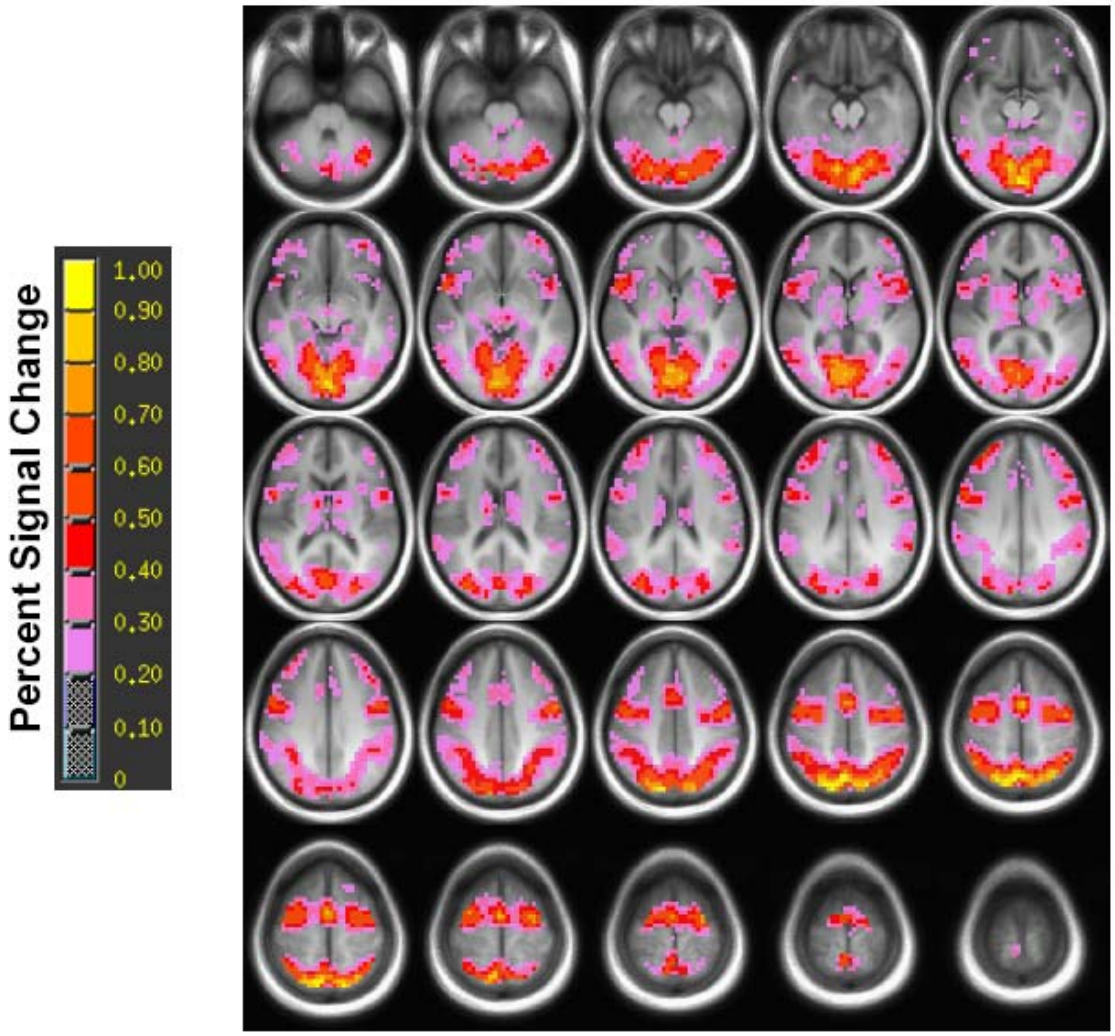


Figure 4.52 Antisaccade-related activity during Antisaccade/Fixation Paradigm at Pre-Test. Functional magnetic resonance imaging results – whole-brain analysis results for all groups at Pre-Test. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying regions with significant percent signal increase (indicated by the color scale) associated with antisaccade performance in all group across all Pre-Test. The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).

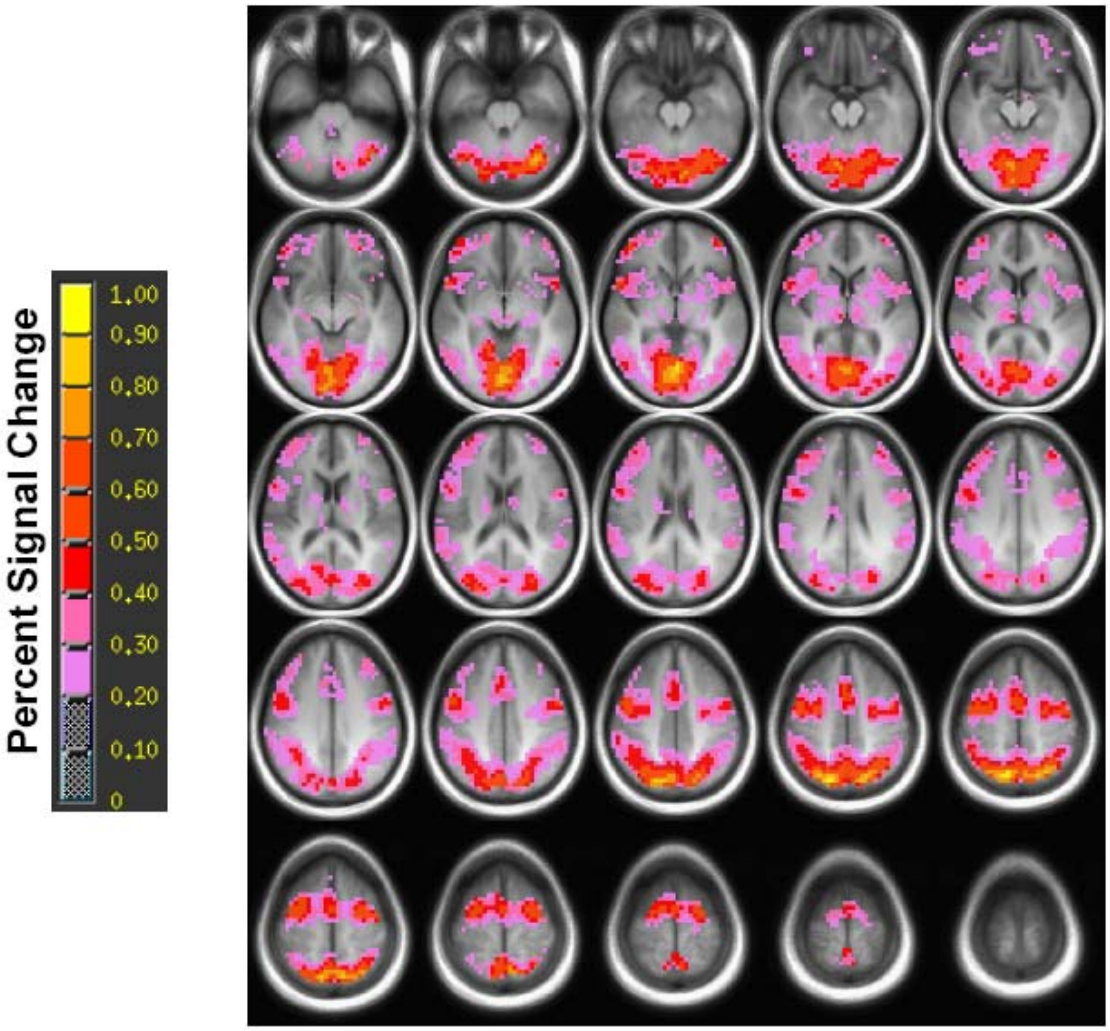


Figure 4.53 Antisaccade-related activity during Antisaccade/Fixation Paradigm at Mid-Test. Functional magnetic resonance imaging results – whole-brain analysis results for all groups at Mid-Test. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying regions with significant percent signal increase (indicated by the color scale) associated with antisaccade performance in all group across all Mid-Test. The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).

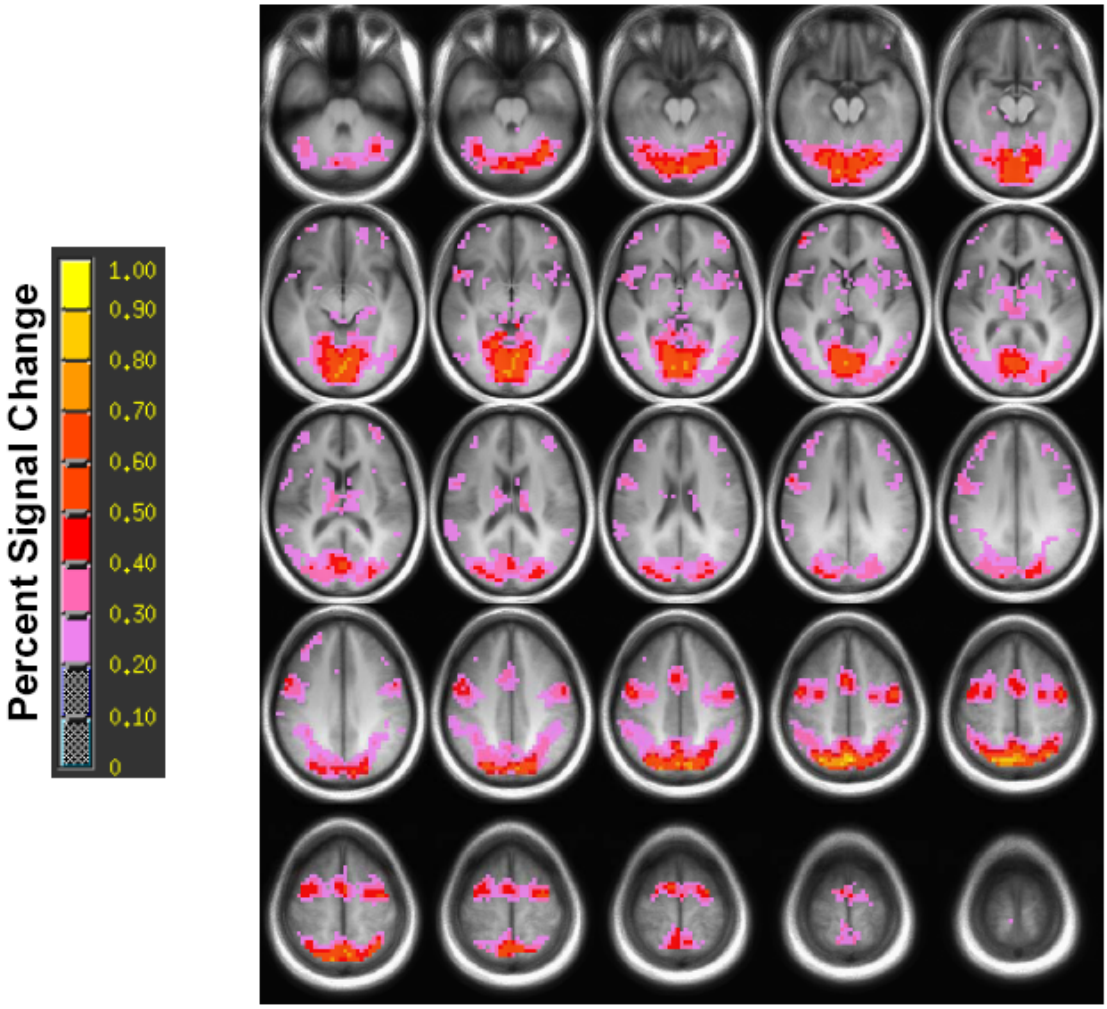


Figure 4.54 Antisaccade-related activity during Antisaccade/Fixation Paradigm at Post-Test. Functional magnetic resonance imgaging results – whole-brain analysis results for all groups at Post-Test. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying regions with significant percent signal increase (indicated by the color scale) associated with antisaccade performance in all group across all Post-Test. The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).

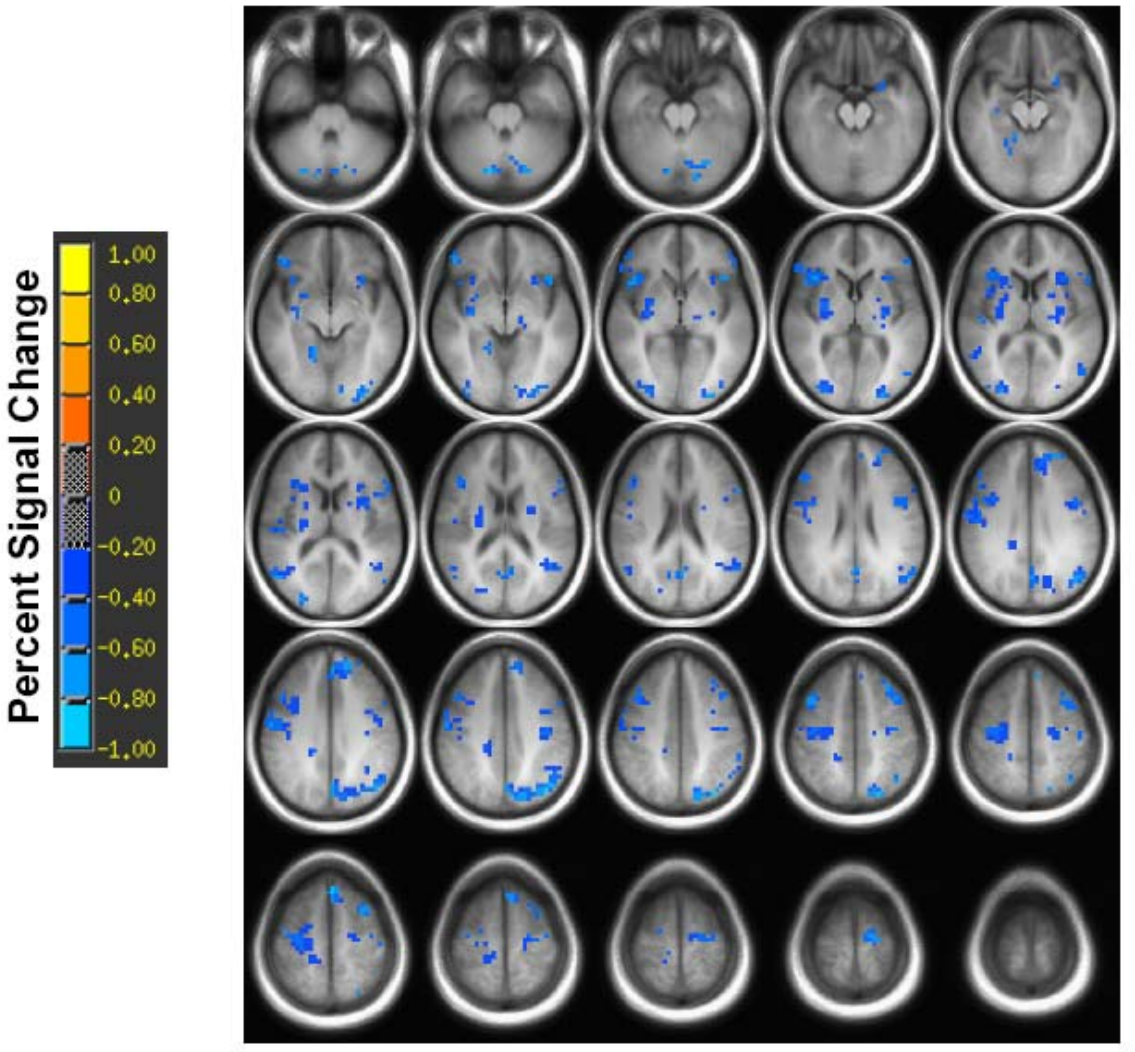


Figure 4.55 FMRI: Differences in Diagnosis Group. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying significant differences between the normal and schizophrenia groups during performance of the antisaccade/fixation paradigm collapsed over time. Regions in which the normal group demonstrated greater activity are shown in cool colors, regions in which the schizophrenia group demonstrated greater activity are shown in warm colors (none). The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).

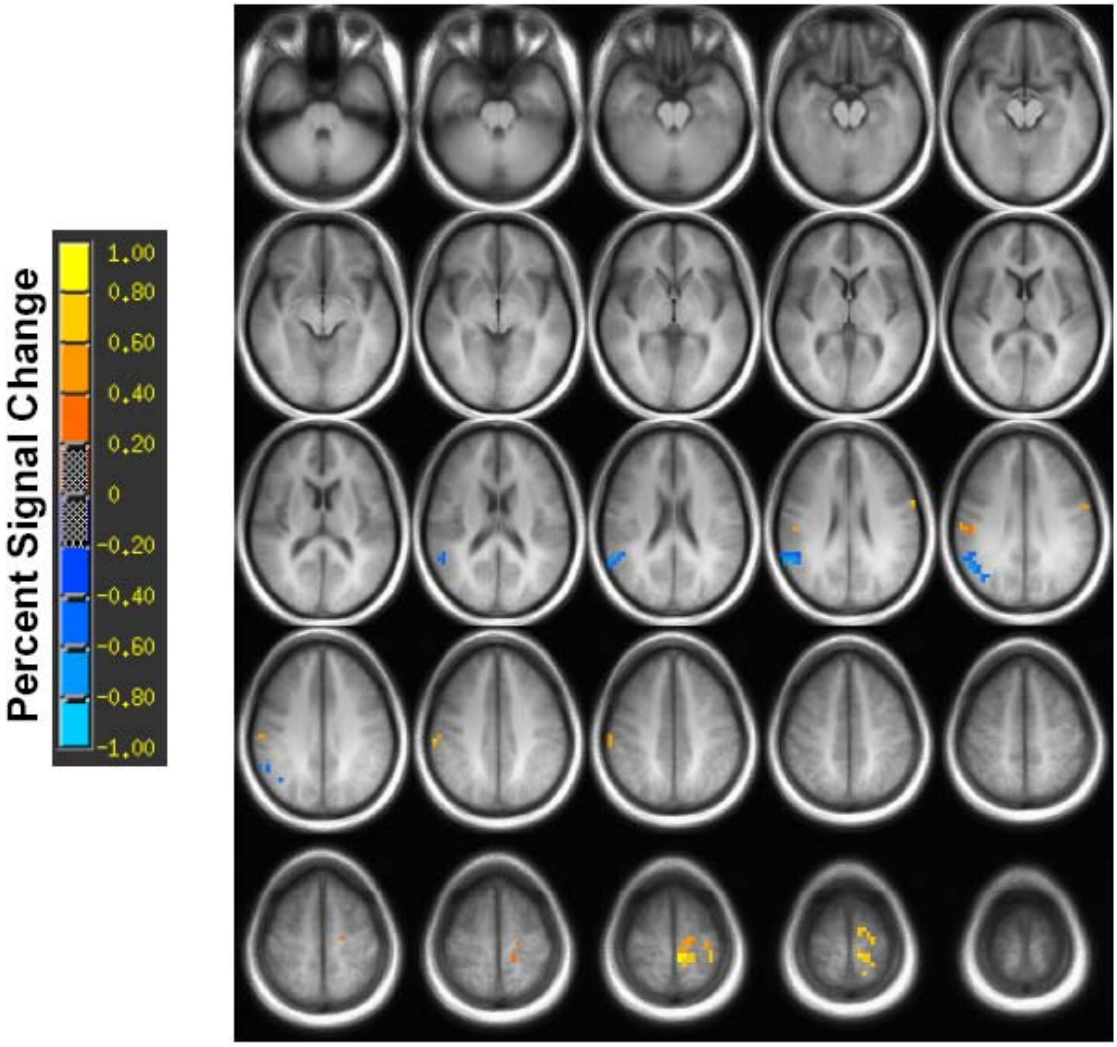


Figure 4.56 FMRI: Differences in Practice Group. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying significant differences between the prosaccade- and antisaccade-practice groups during performance of the antisaccade/fixation paradigm collapsed over time. Regions in which the prosaccade practice group demonstrated greater activity are shown in cool colors, regions in which the antisaccade practice group demonstrated greater activity are shown in warm colors. The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).

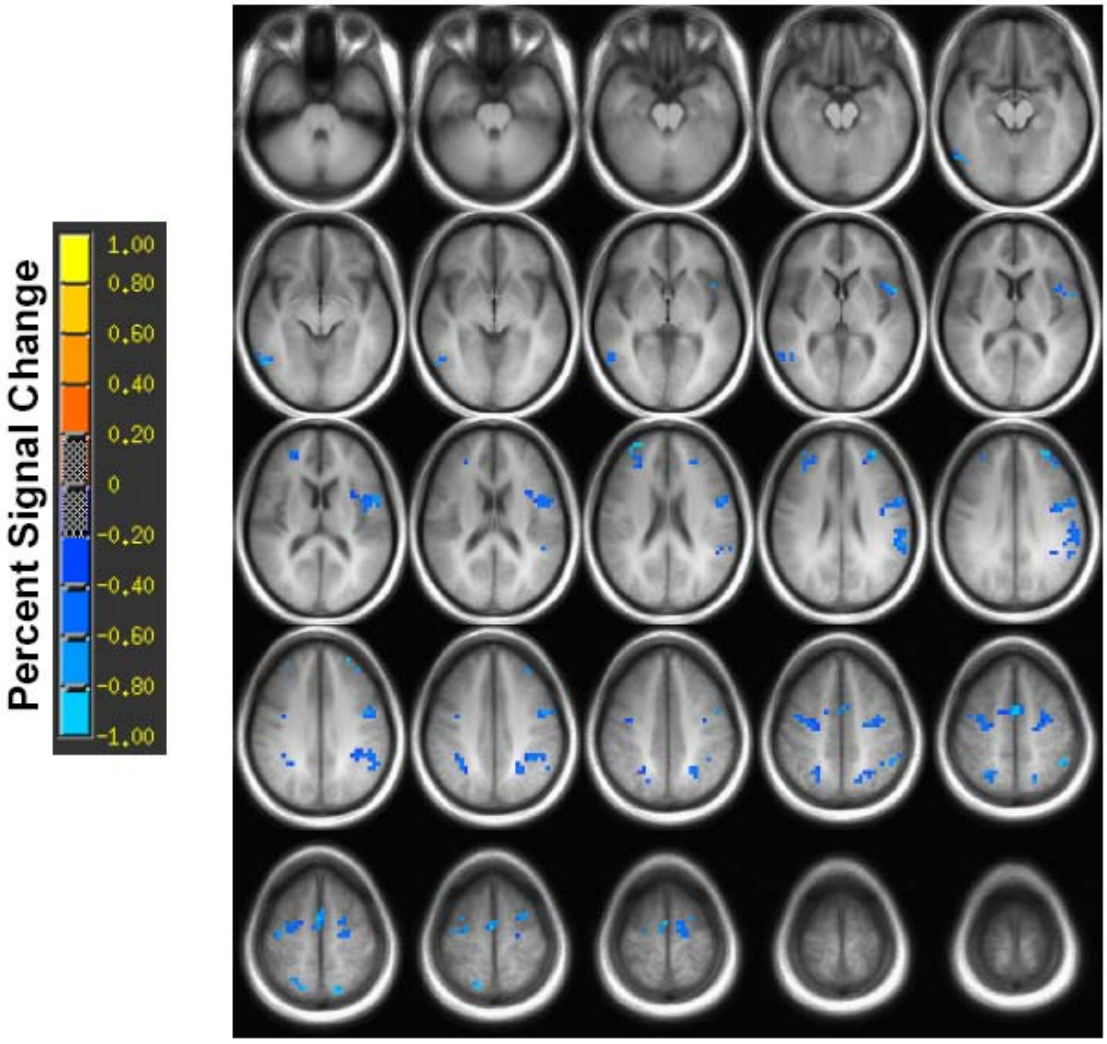


Figure 4.57 FMRI: Differences from Pre-Test to Post-Test. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying significant differences between Pre-Test and Post-Test during performance of the antisaccade/fixation paradigm collapsed across all groups. Regions in which greater activity was demonstrated at Pre-Test are shown in cool colors, regions in greater activity was demonstrated at Post-Test are shown in warm colors. The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).

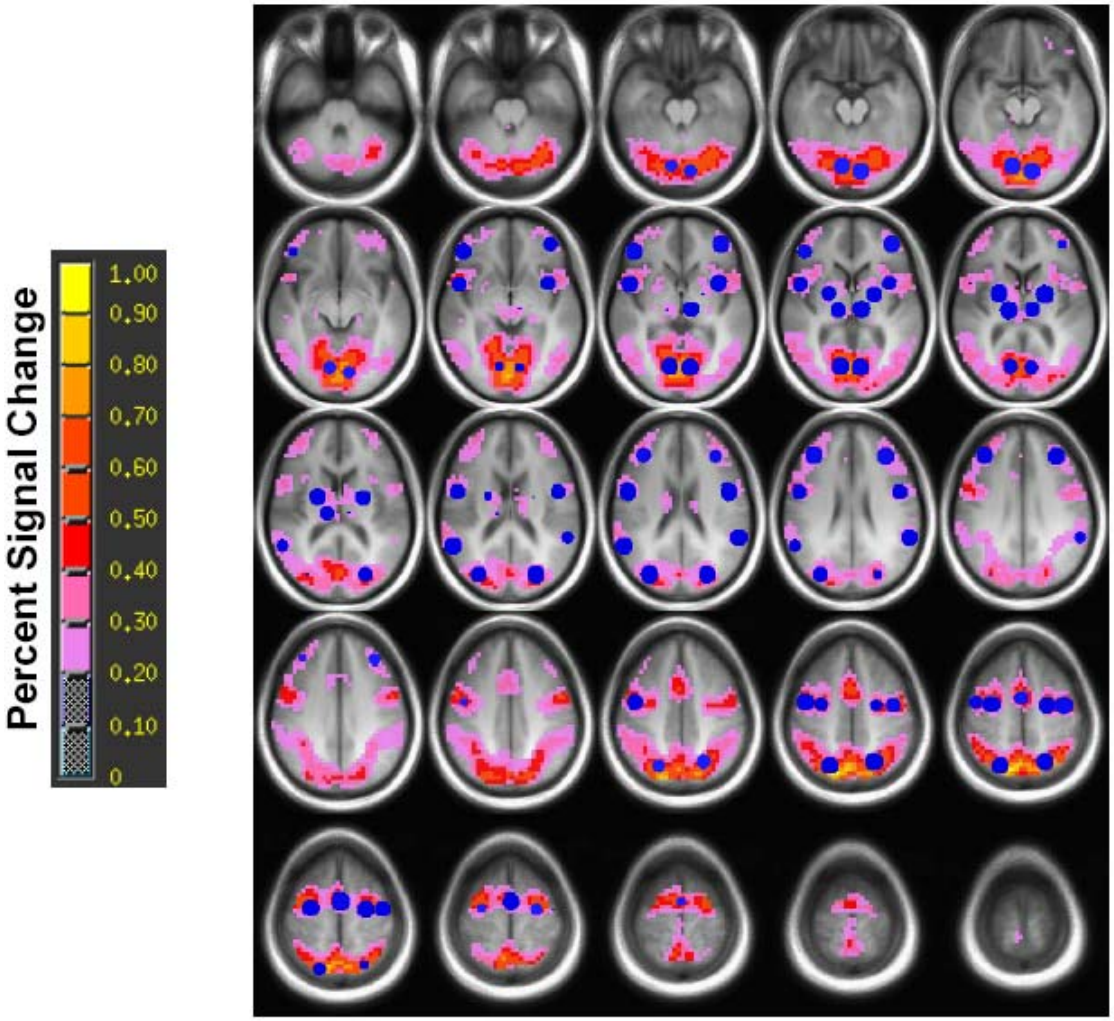
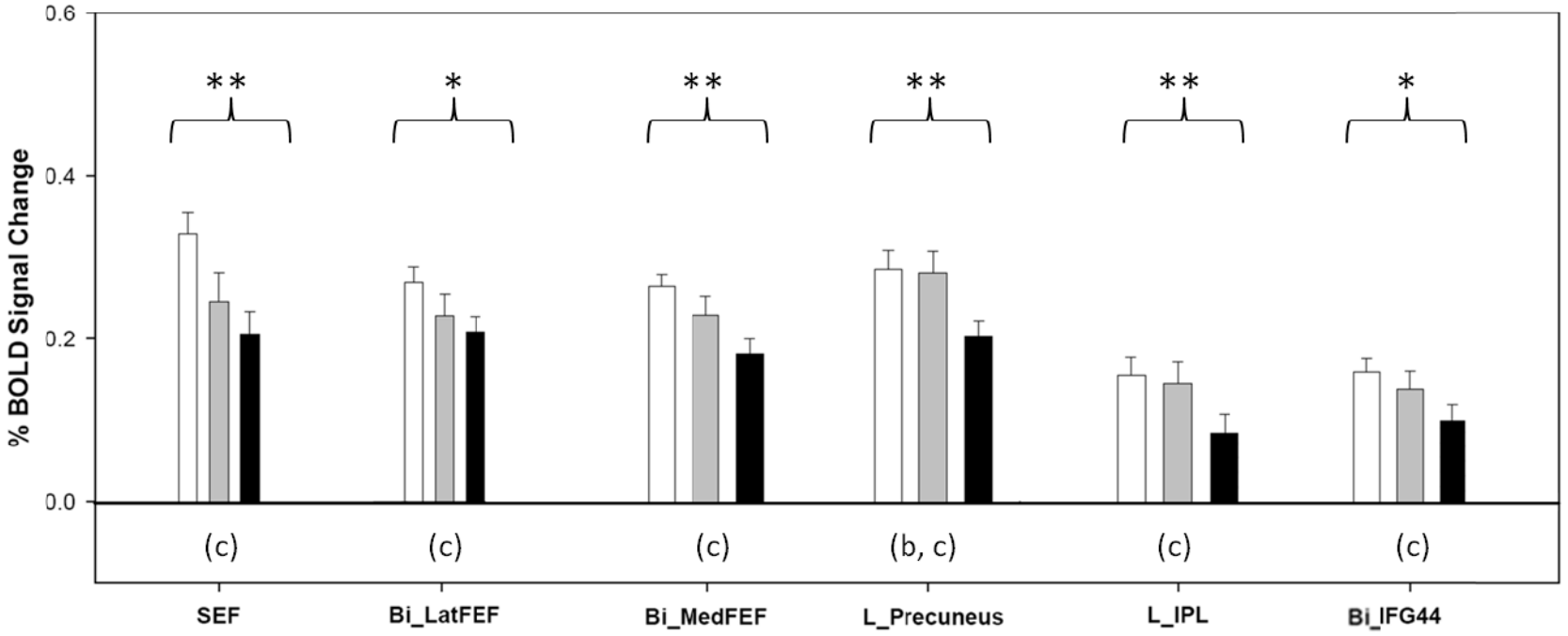


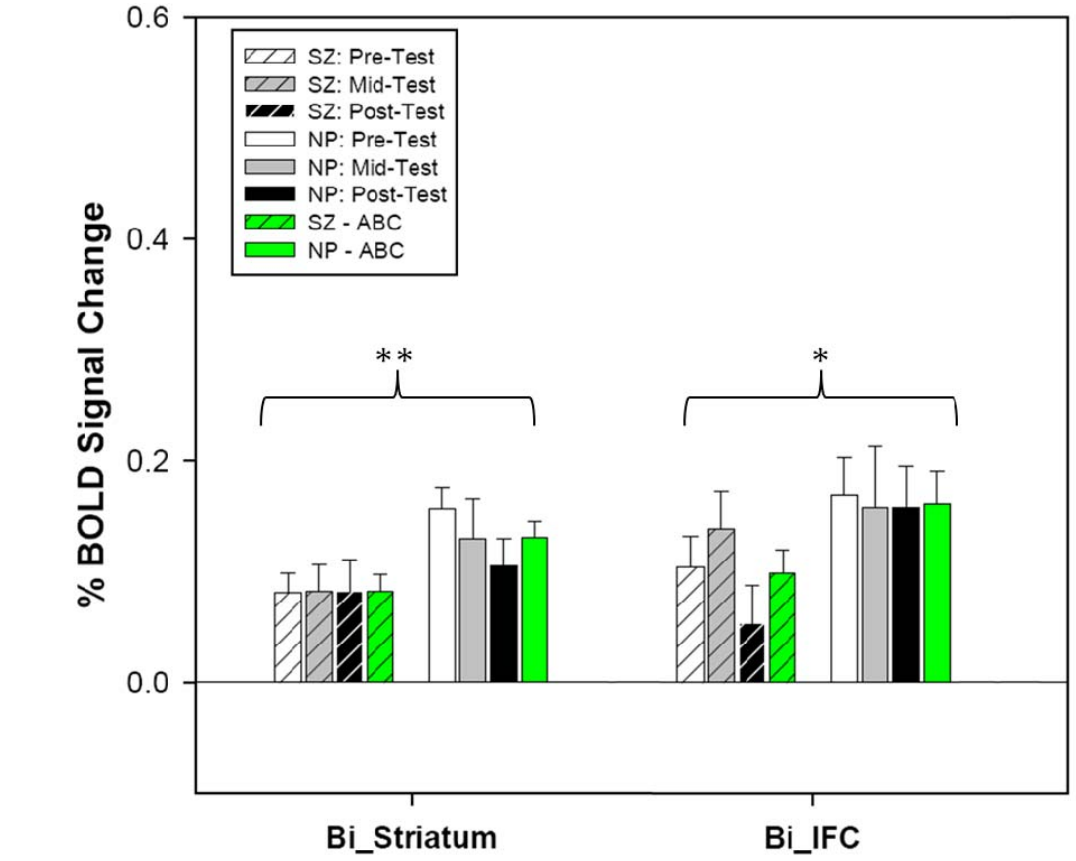
Figure 4.58 ROI Overlay. Axial slices (top left z = -26 through bottom right z = 70, spacing = 4mm) displaying regions with significant percent signal increase (indicated by the color scale) associated with antisaccade performance in all group across all timepoints. ROIs (shown in blue) were drawn at the center of mass of each activated region. The background anatomical image is the average structural image from 55 participants in radiological convention (left-hemisphere on the right).



Error Bars: +/- 1 Standard Error

** Significant Effect of Time ($p < 0.05$)
* Trend-level Effect of Time ($0.05 < p < 0.10$)
a Significant decrease between Pre-Test and Mid-Test
b Significant decrease between Mid-Test and Post-Test
c Significant decrease between Pre-Test and Post-Test

Figure 4.59 ROIs Demonstrating Main Effect of Time.



Error Bars: +/- 1 Standard Error

** Significan: Effect of Diagnosis ($p < 0.05$)

* Trend-level Effect of Diagnosis ($0.05 < p < 0.10$)

Figure 4.60 ROIs Demonstrating Main Effect of Diagnosis Group.

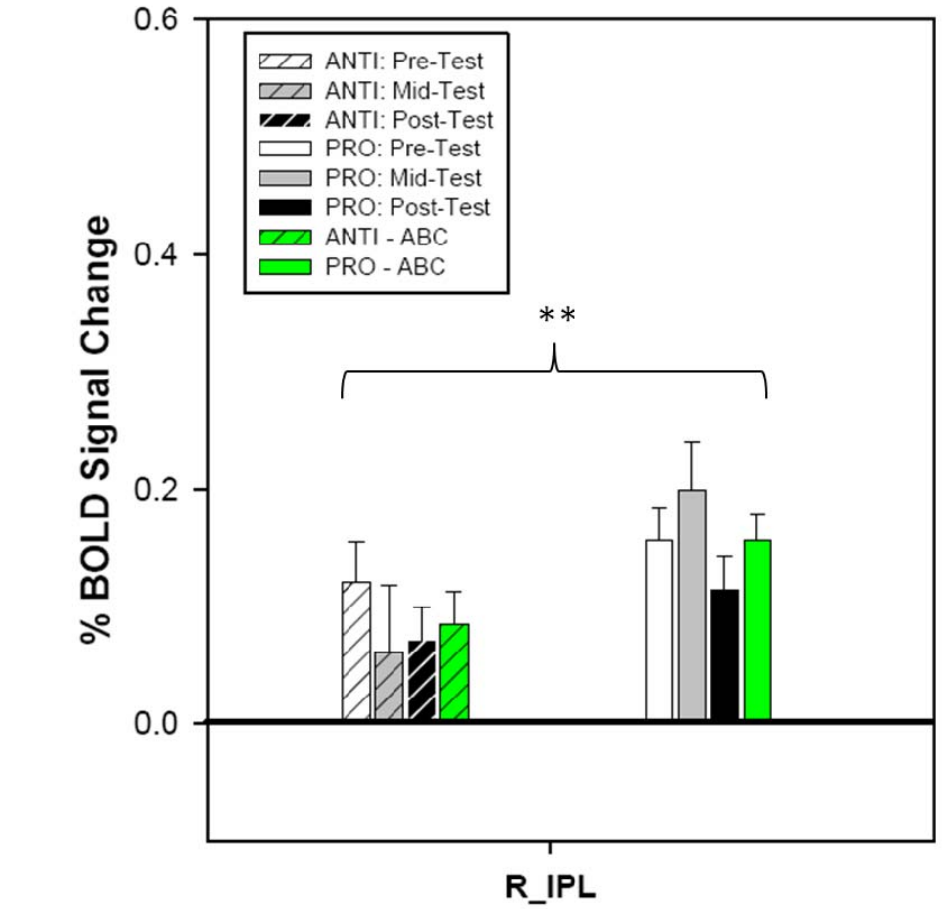


Figure 4.61 ROIs Demonstrating Main Effect of Practice Group.

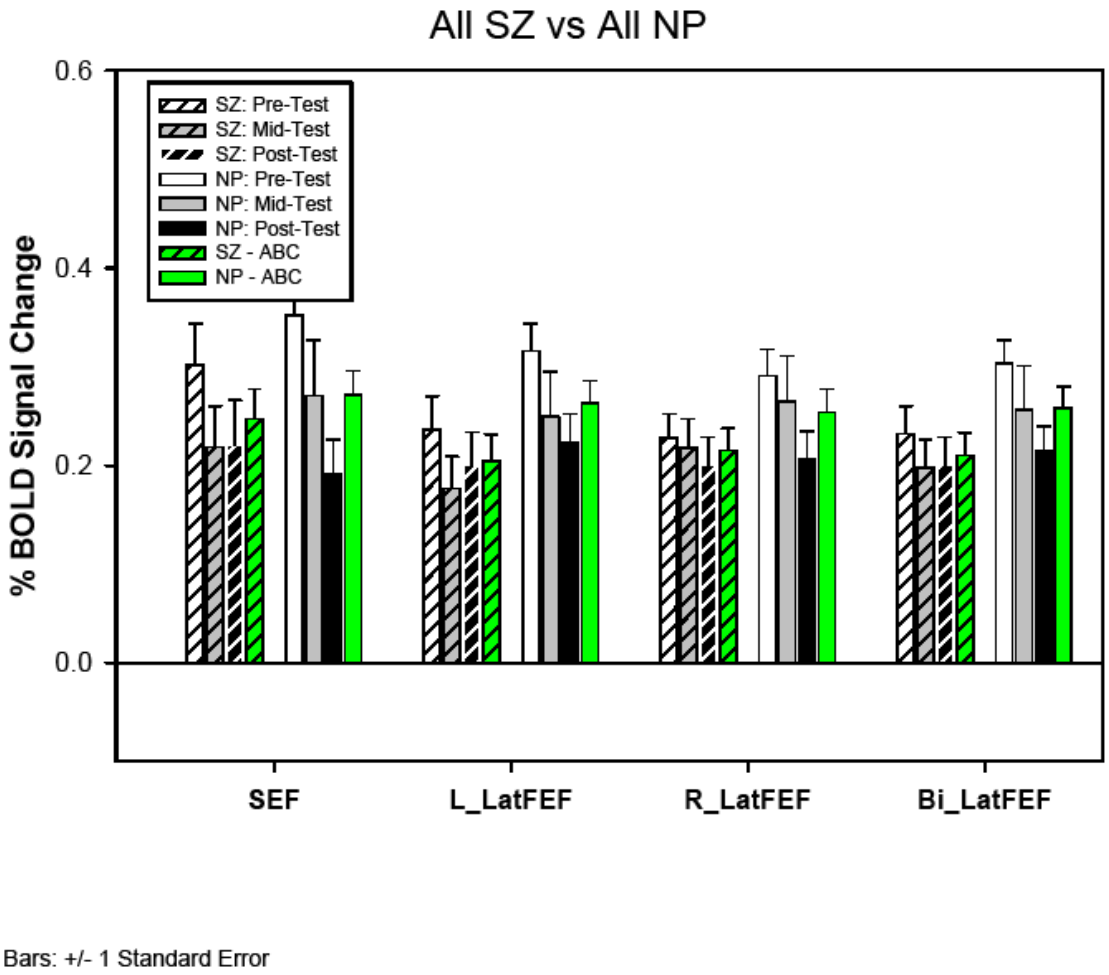


Figure 4.62 ROI s – SZ vs NP 1

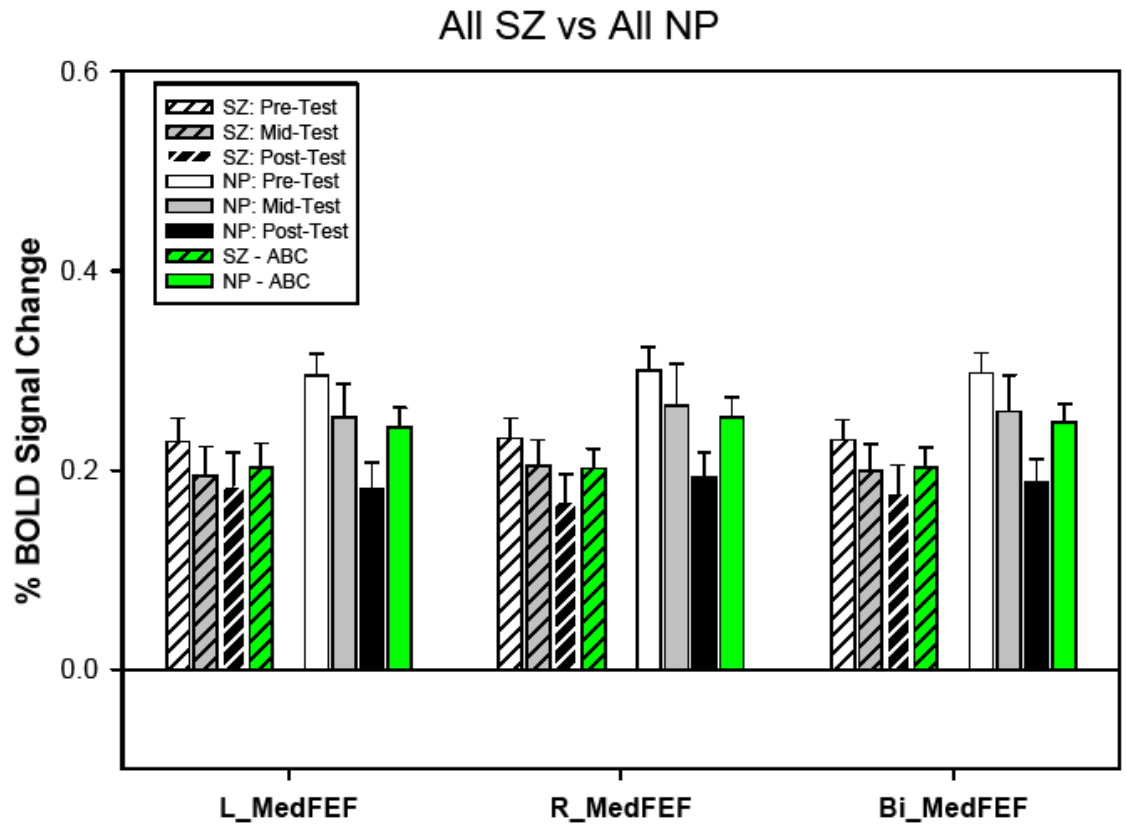


Figure 4.63 ROI s – SZ vs NP 2

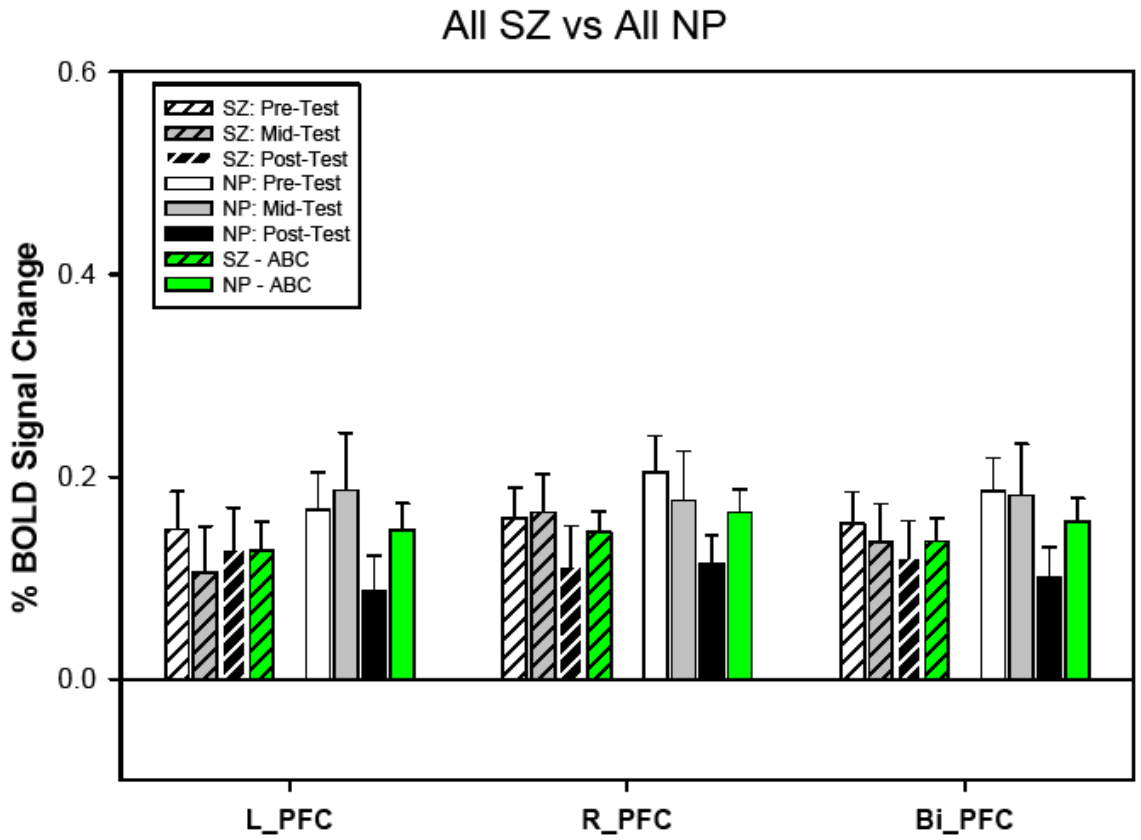


Figure 4.64 **ROI s – SZ vs NP 3**

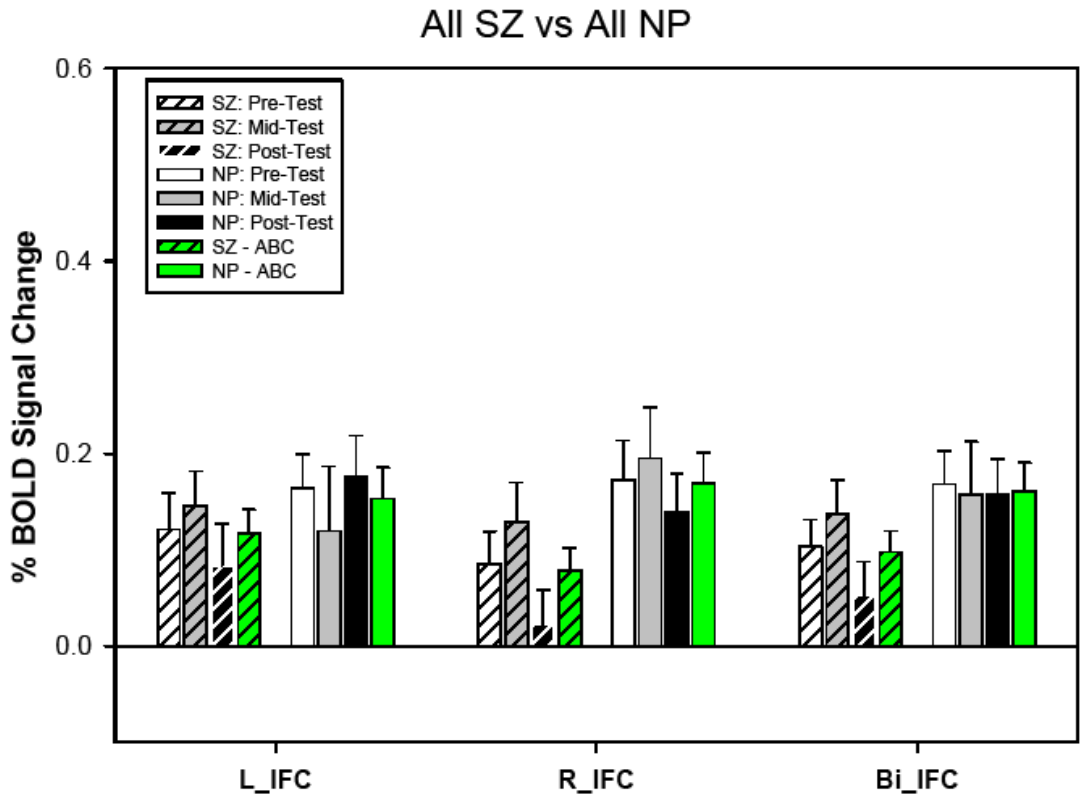


Figure 4.65 ROI s – SZ vs NP 4

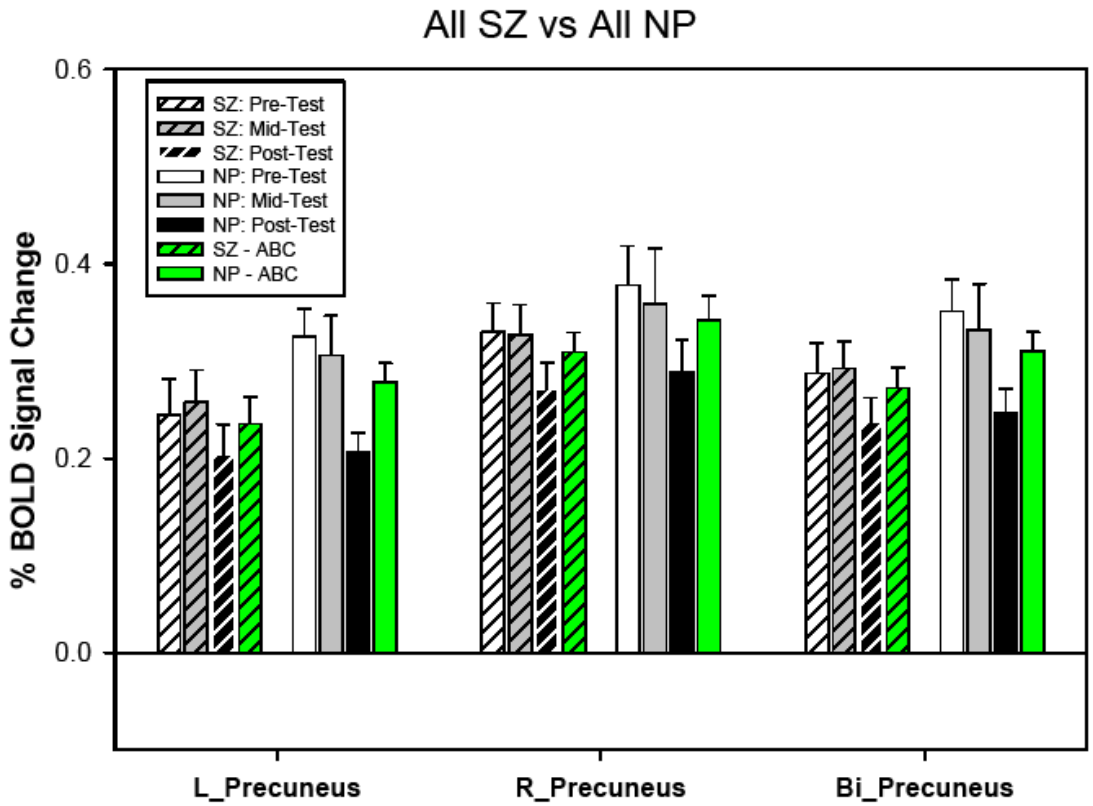


Figure 4.66 ROI s – SZ vs NP 5

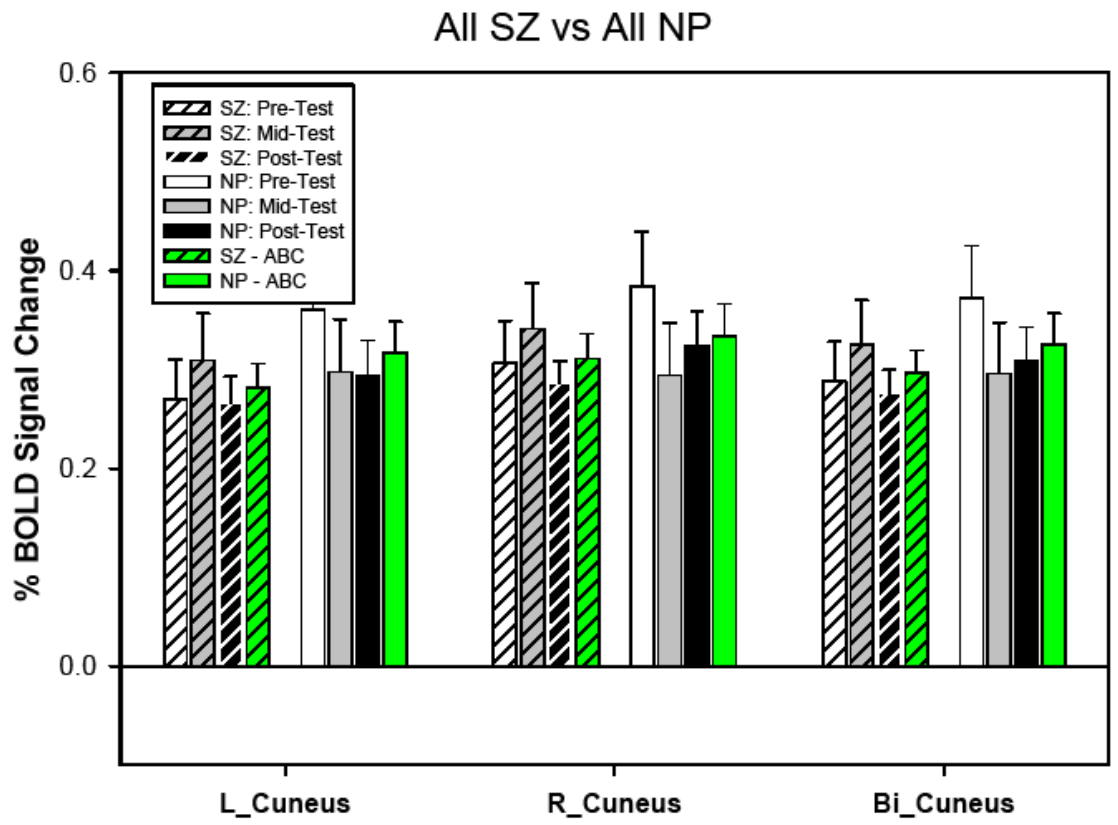


Figure 4.67 **ROI s – SZ vs NP 6**

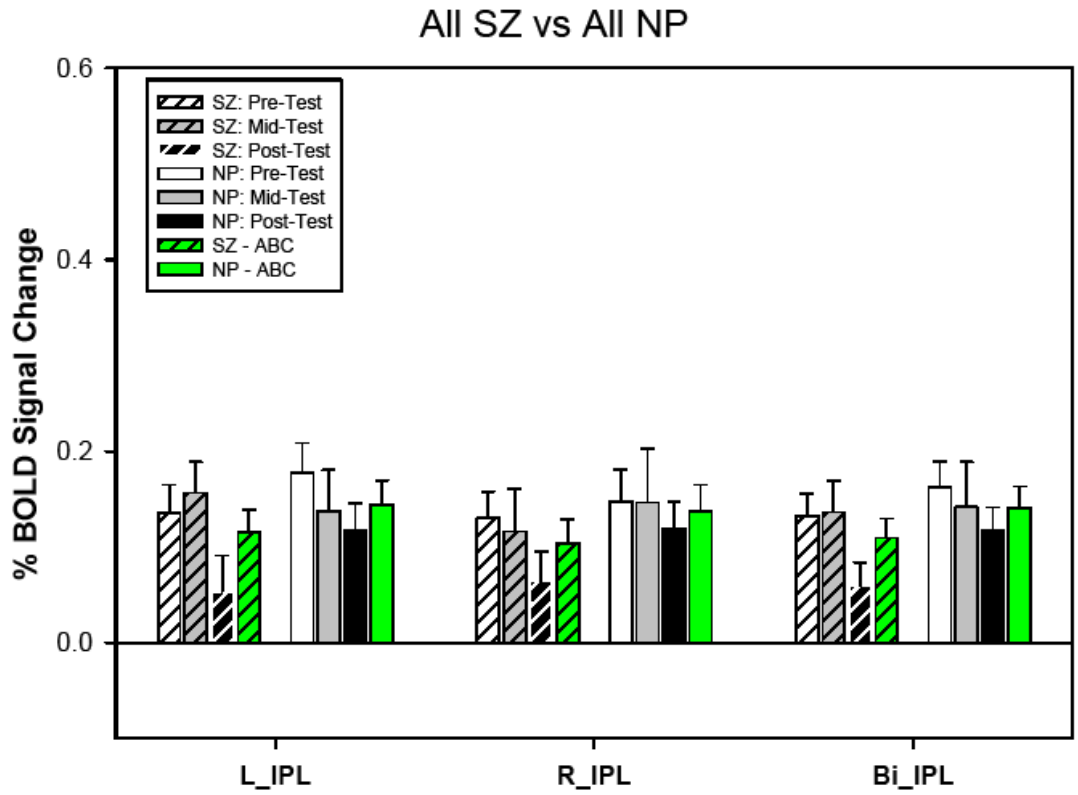


Figure 4.68 **ROI s – SZ vs NP 7**

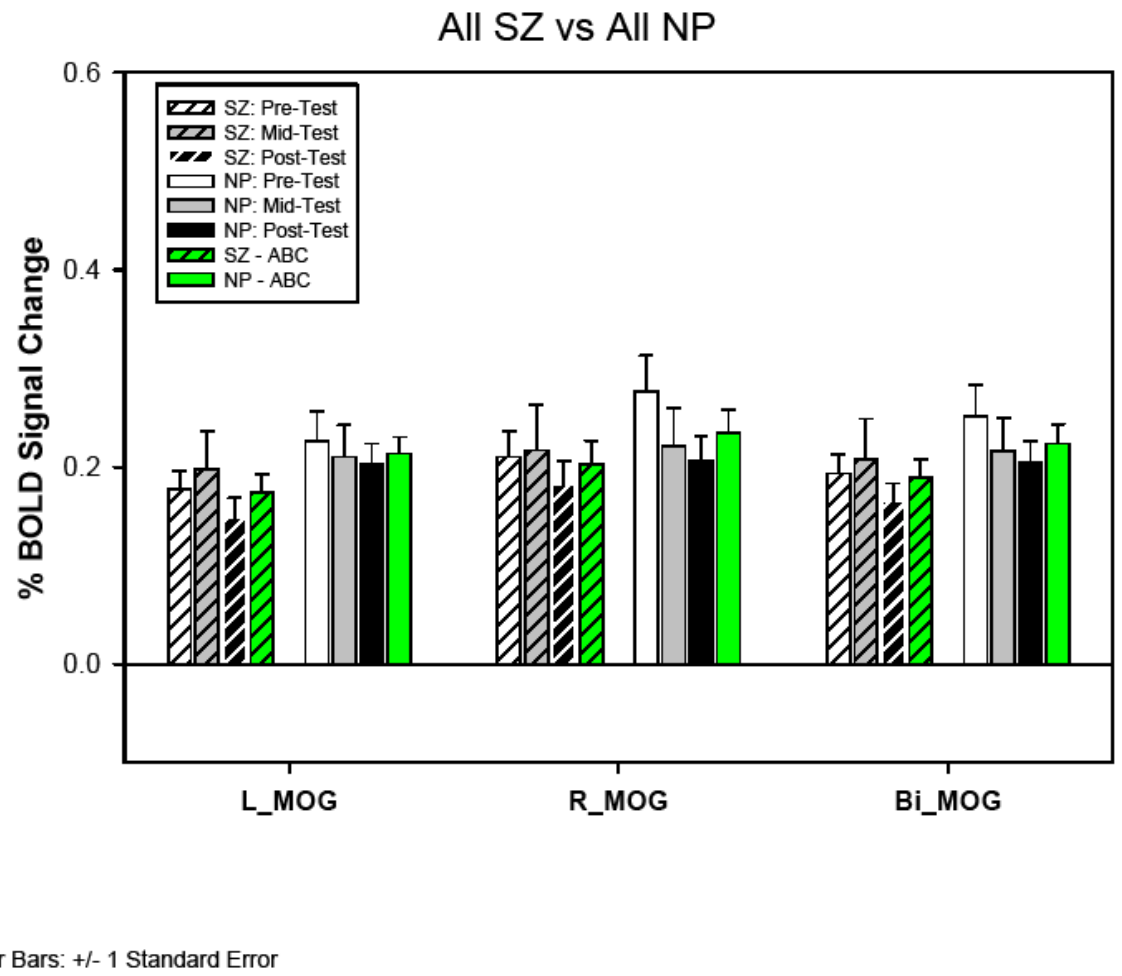


Figure 4.69 ROI s – SZ vs NP 8

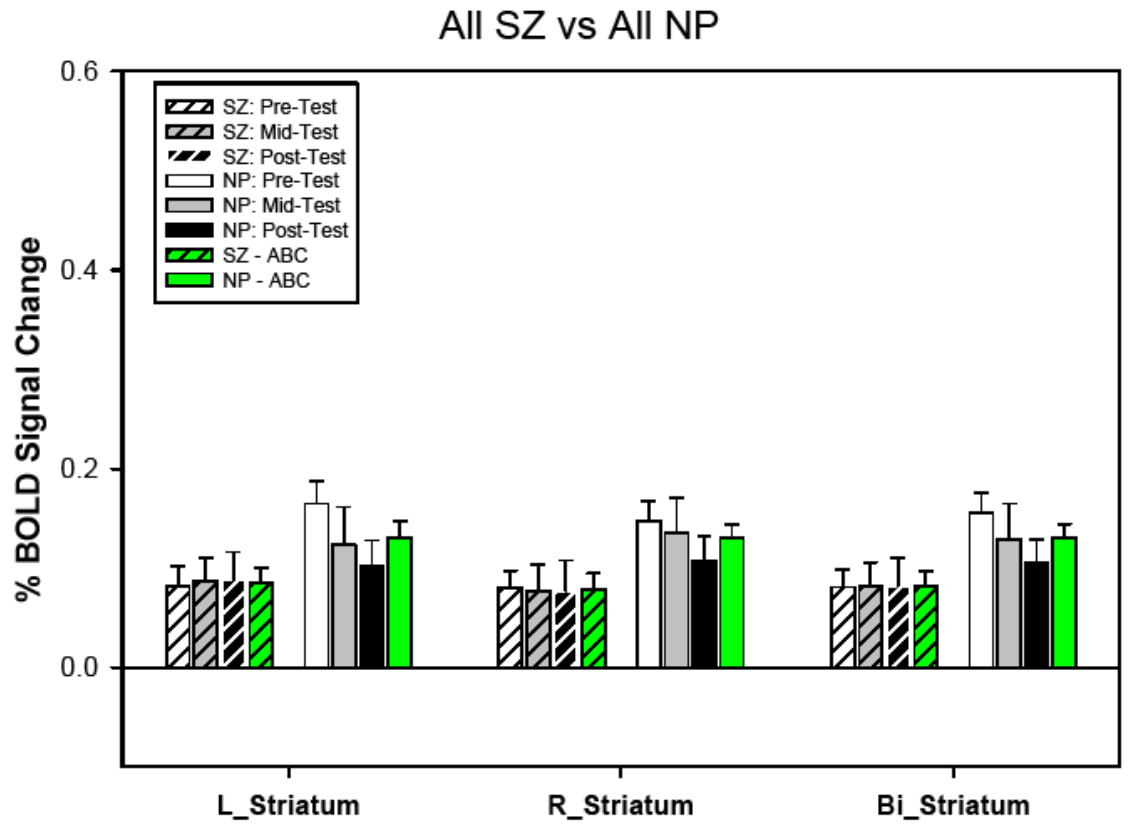


Figure 4.70 ROI s – SZ vs NP 9

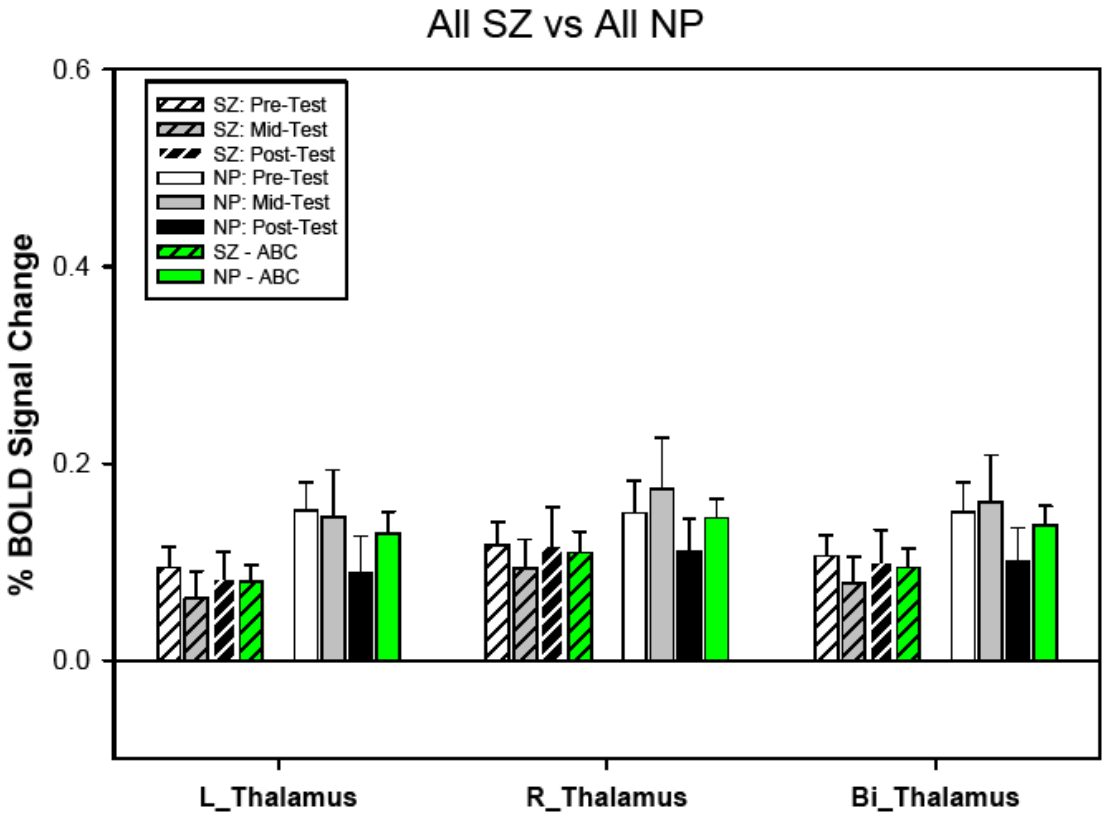


Figure 4.71 ROI s – SZ vs NP 10

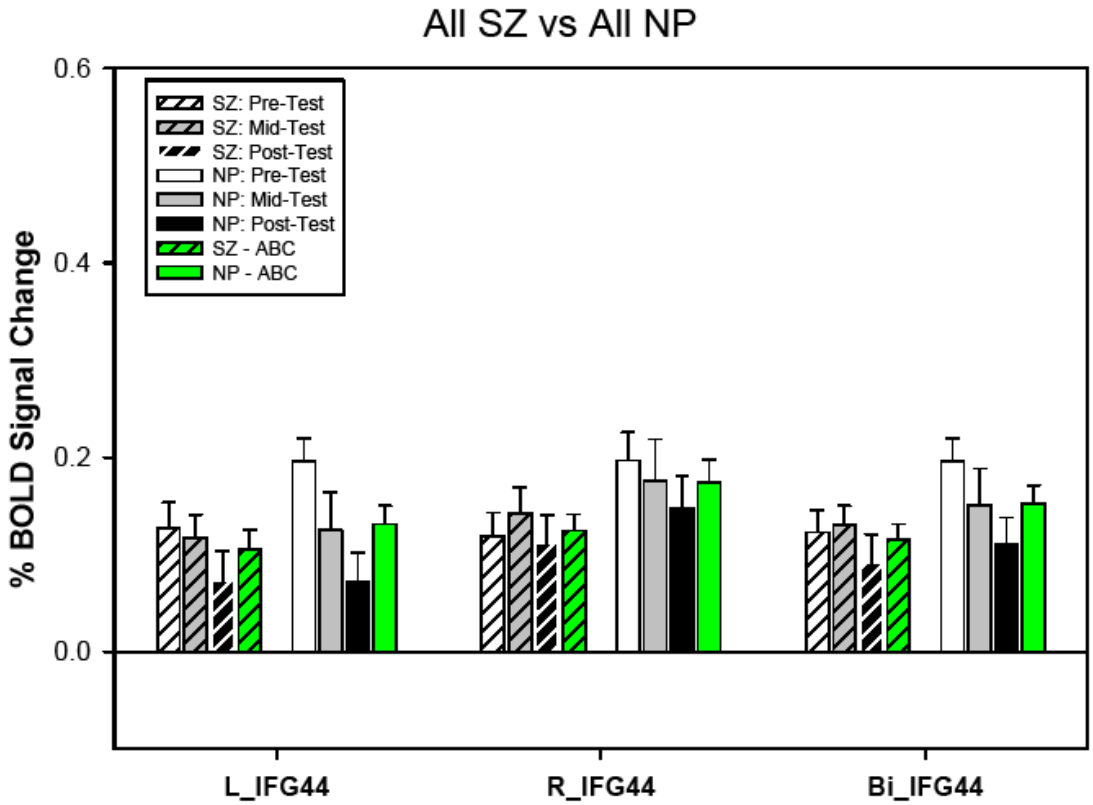


Figure 4.72 ROI s – SZ vs NP 11

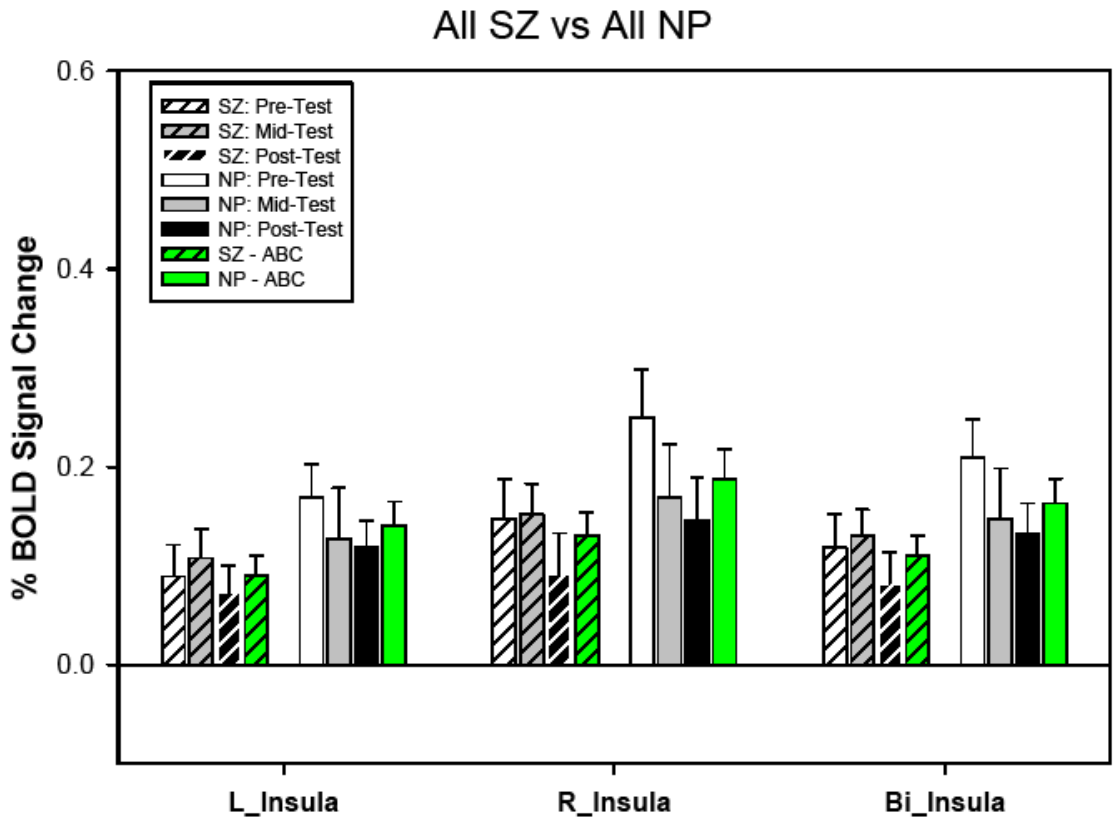


Figure 4.73 ROI s – SZ vs NP 12

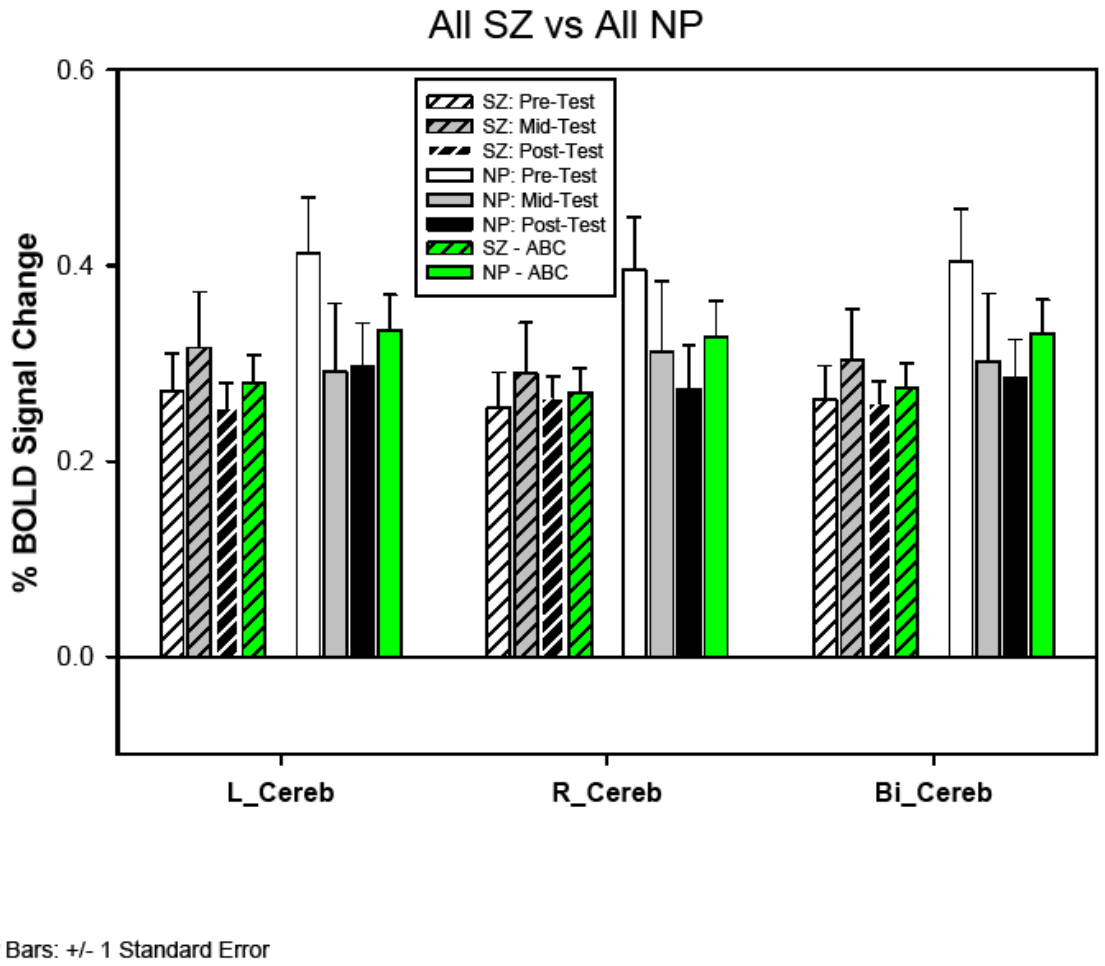


Figure 4.74 ROI s – SZ vs NP 13

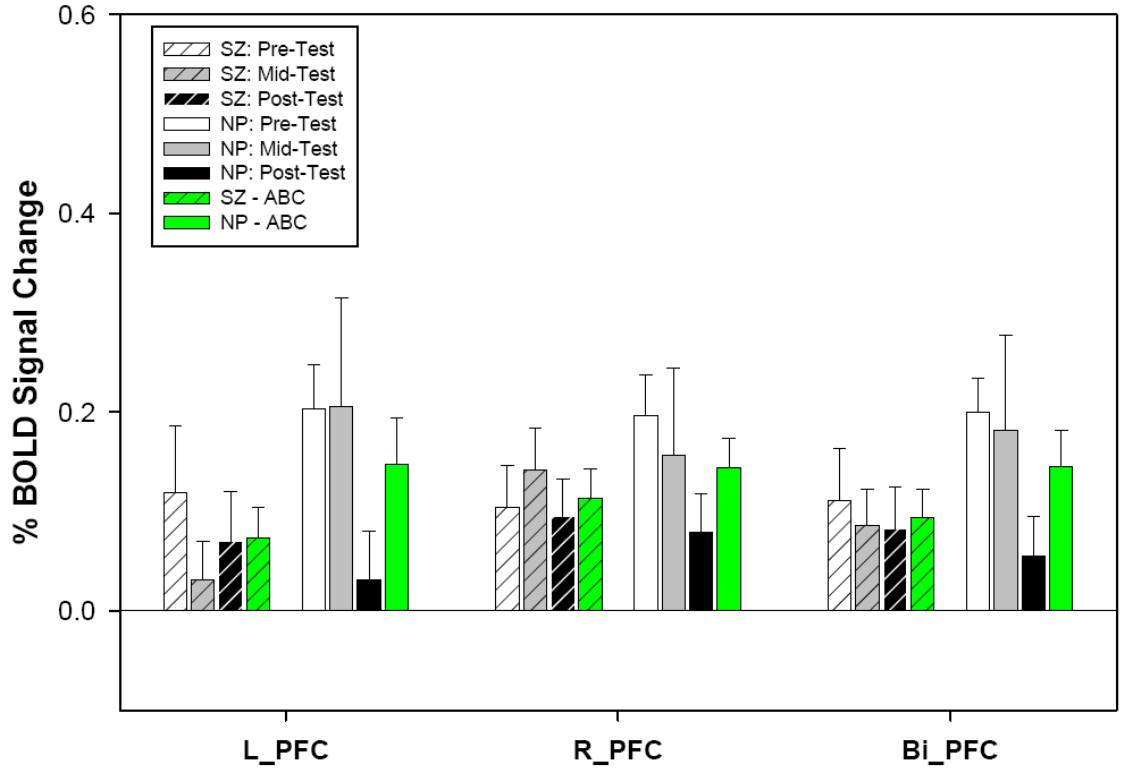


Figure 4.75 PFC Activation for Antisaccade Practice Groups

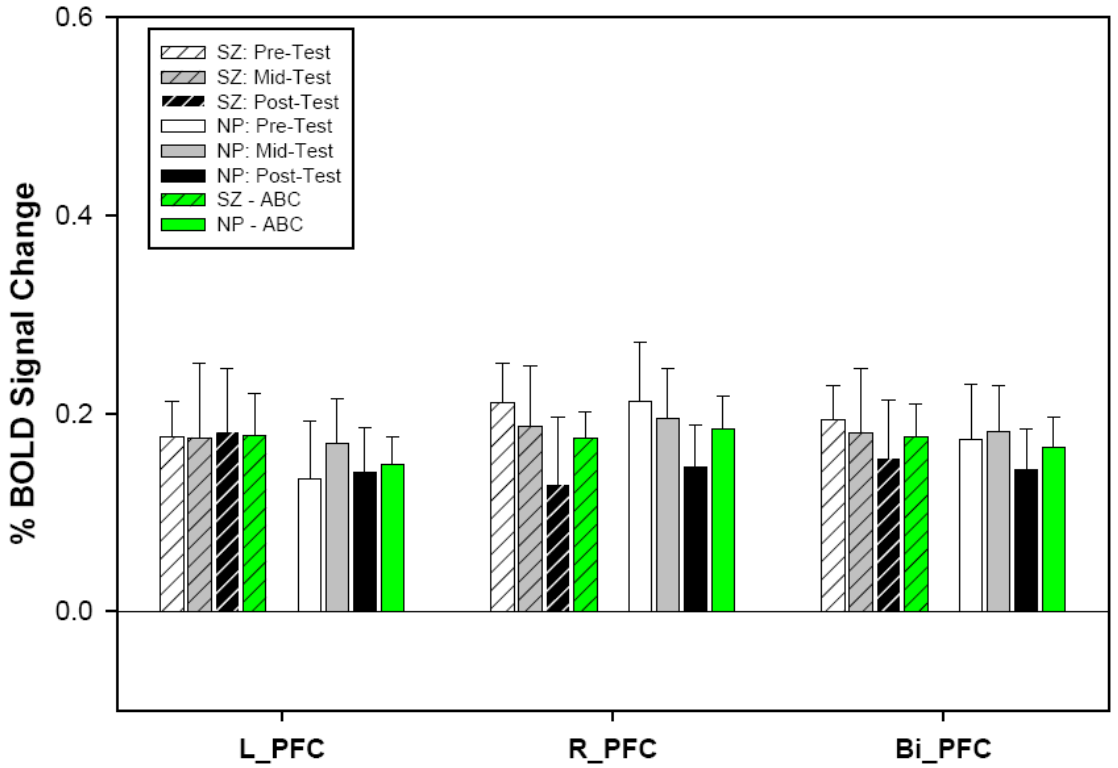
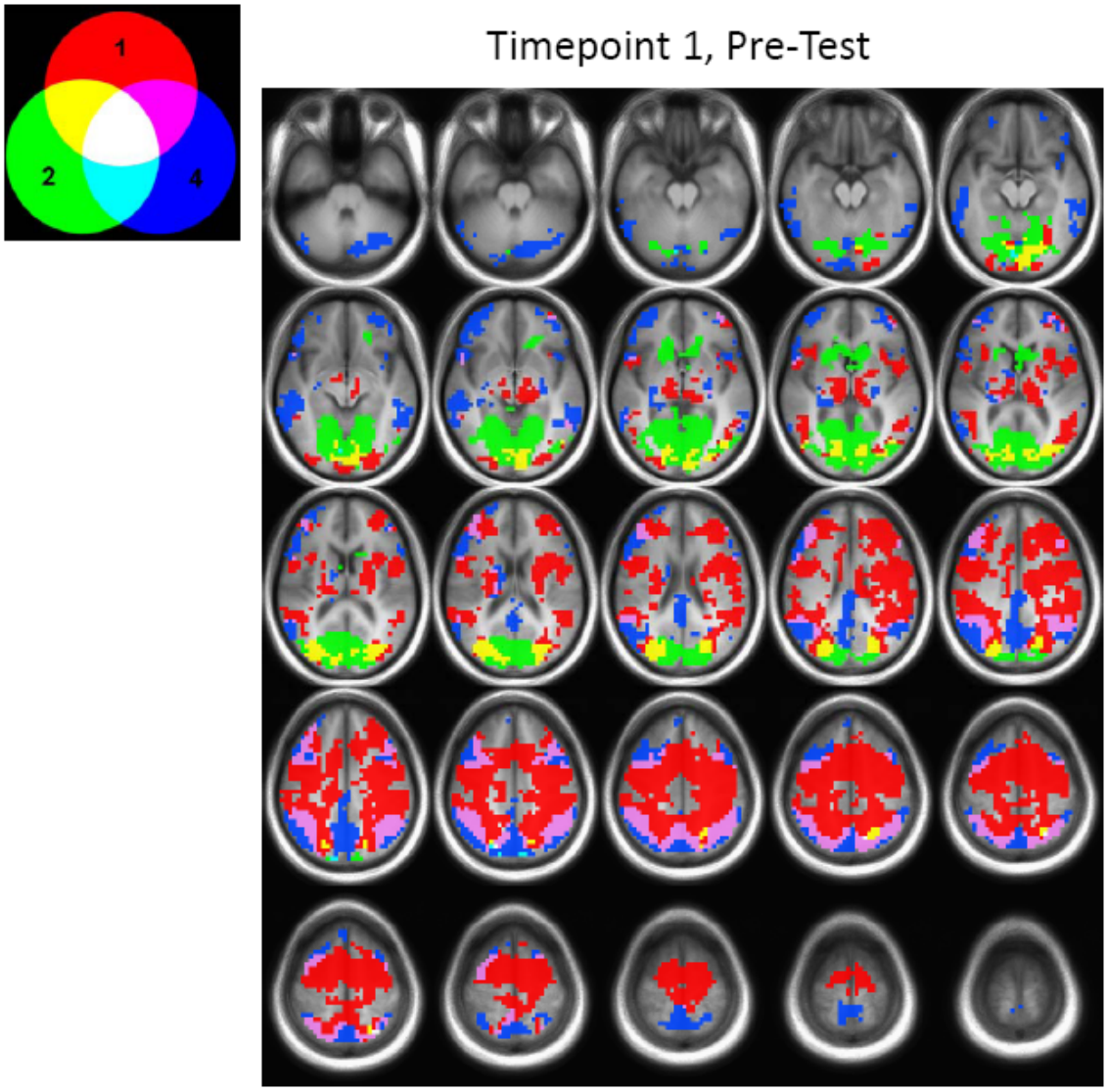


Figure 4.76 PFC Activation for Prosaccade Practice Groups



<u>Figure 4.77</u> Pre-Test Components Analysis at Pre-Test. Shown for all subjects at Pre-Test.

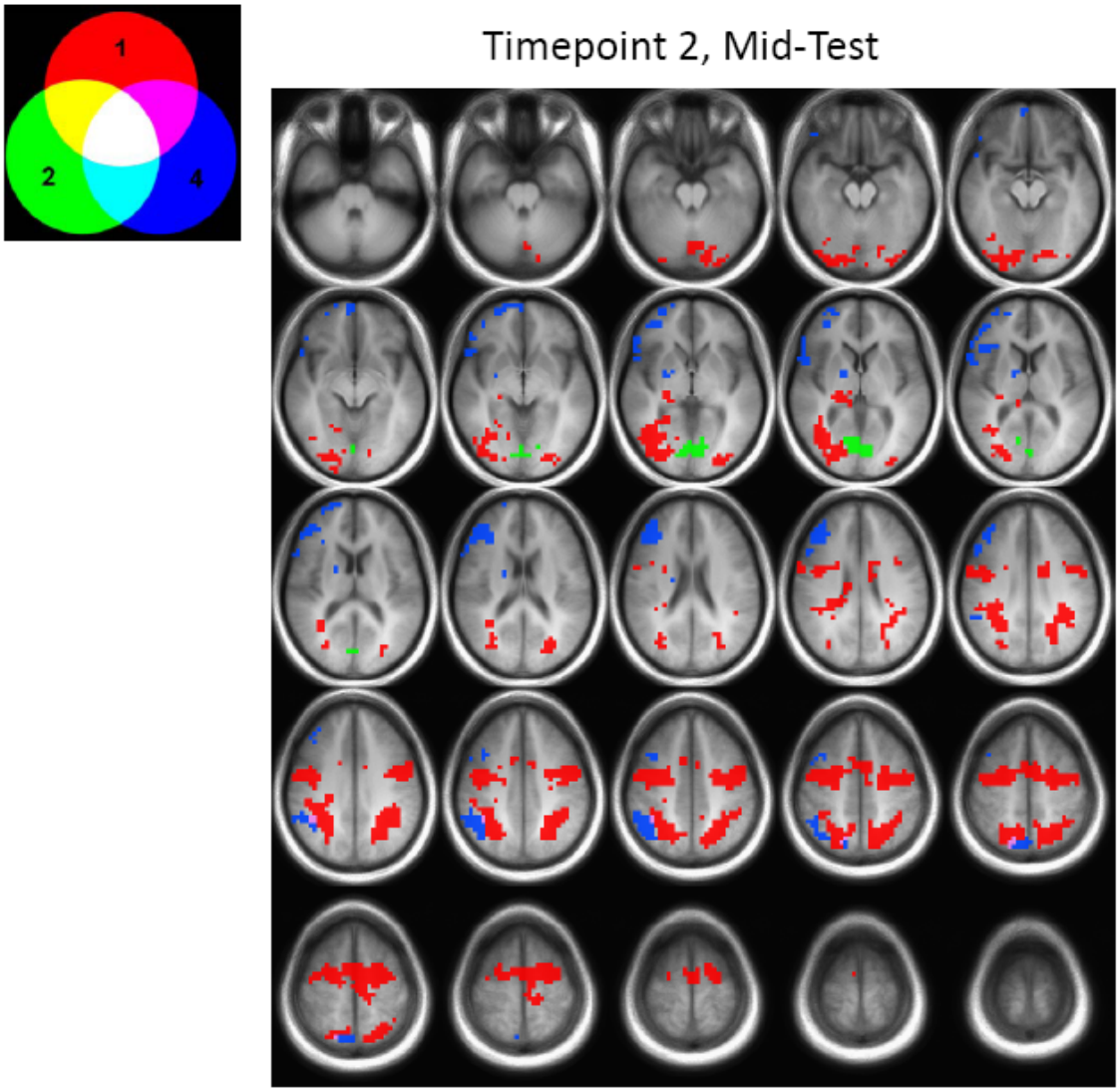


Figure 4.78 Pre-Test Components Analysis at Mid-Test. Shown for all subjects at Mid-Test.

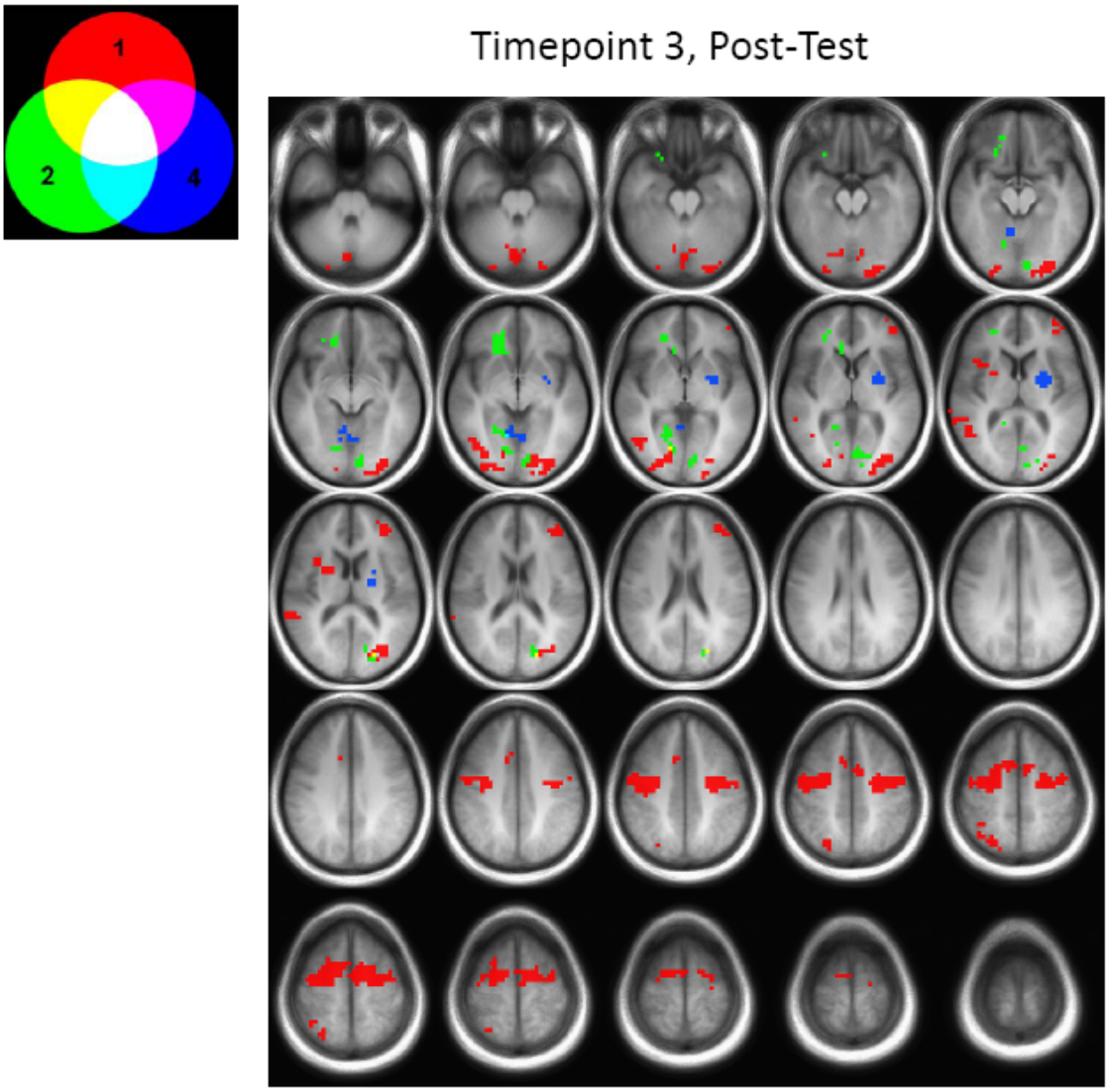


Figure 4.79 Pre-Test Components Analysis at Post-Test. Shown for all subjects at Post-Test.

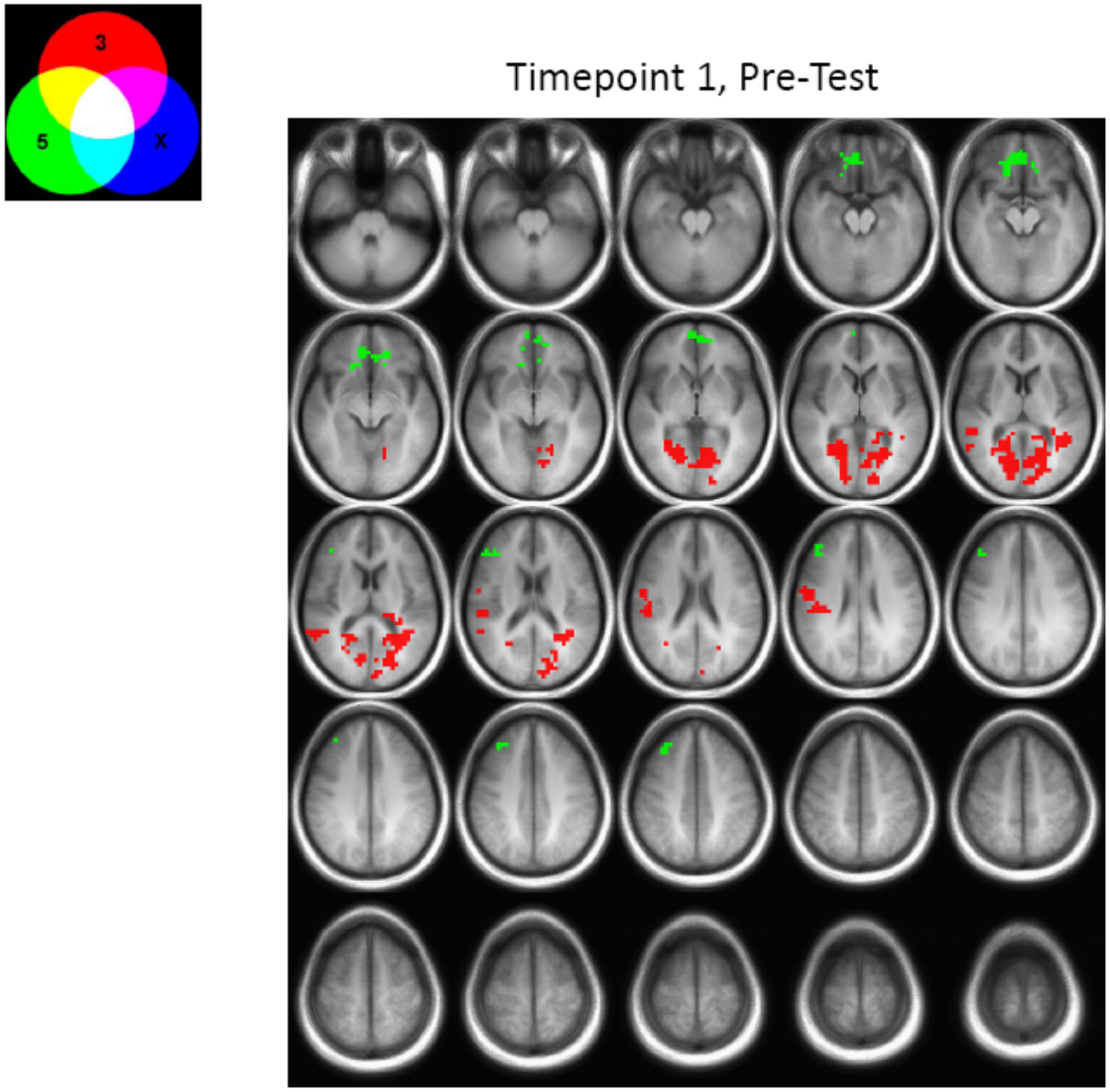
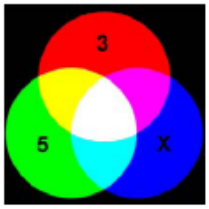


Figure 4.80 Mid-Test Components Analysis at Pre-Test. Shown for all subjects at Pre-Test.



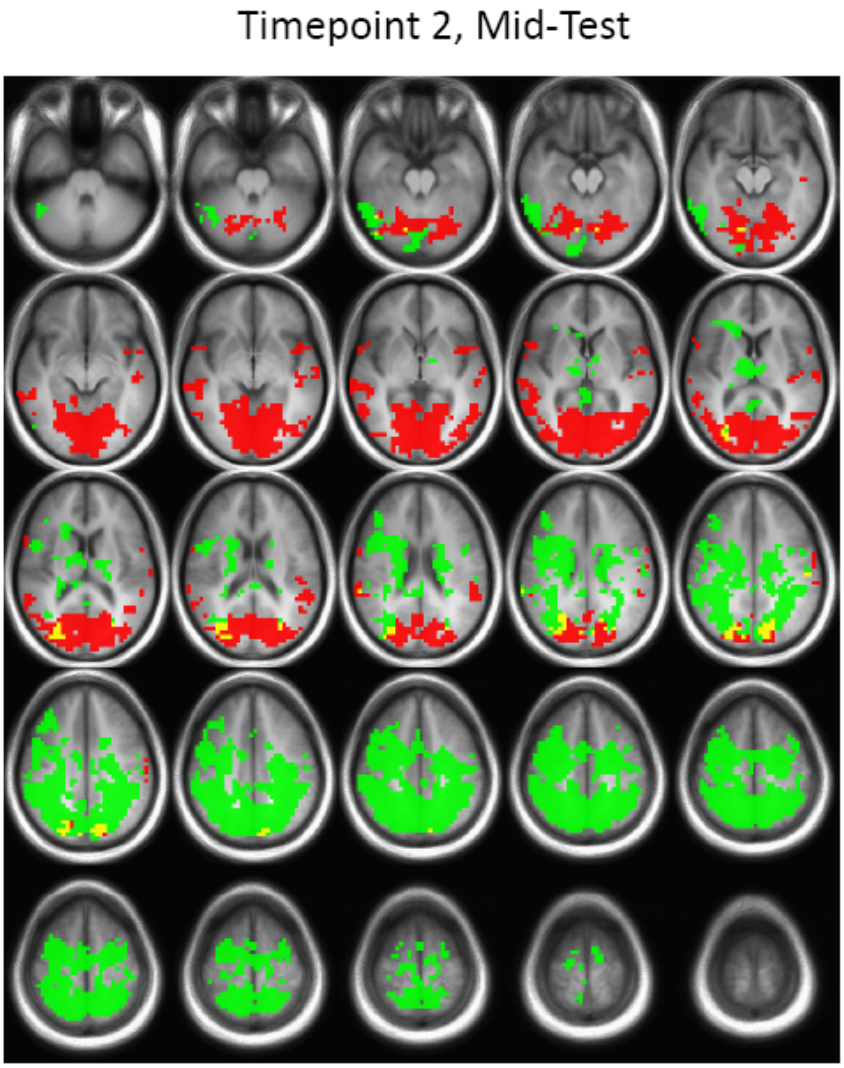


Figure 4.81 Mid-Test Components Analysis at Mid-Test. Shown for all subjects at Mid-Test.

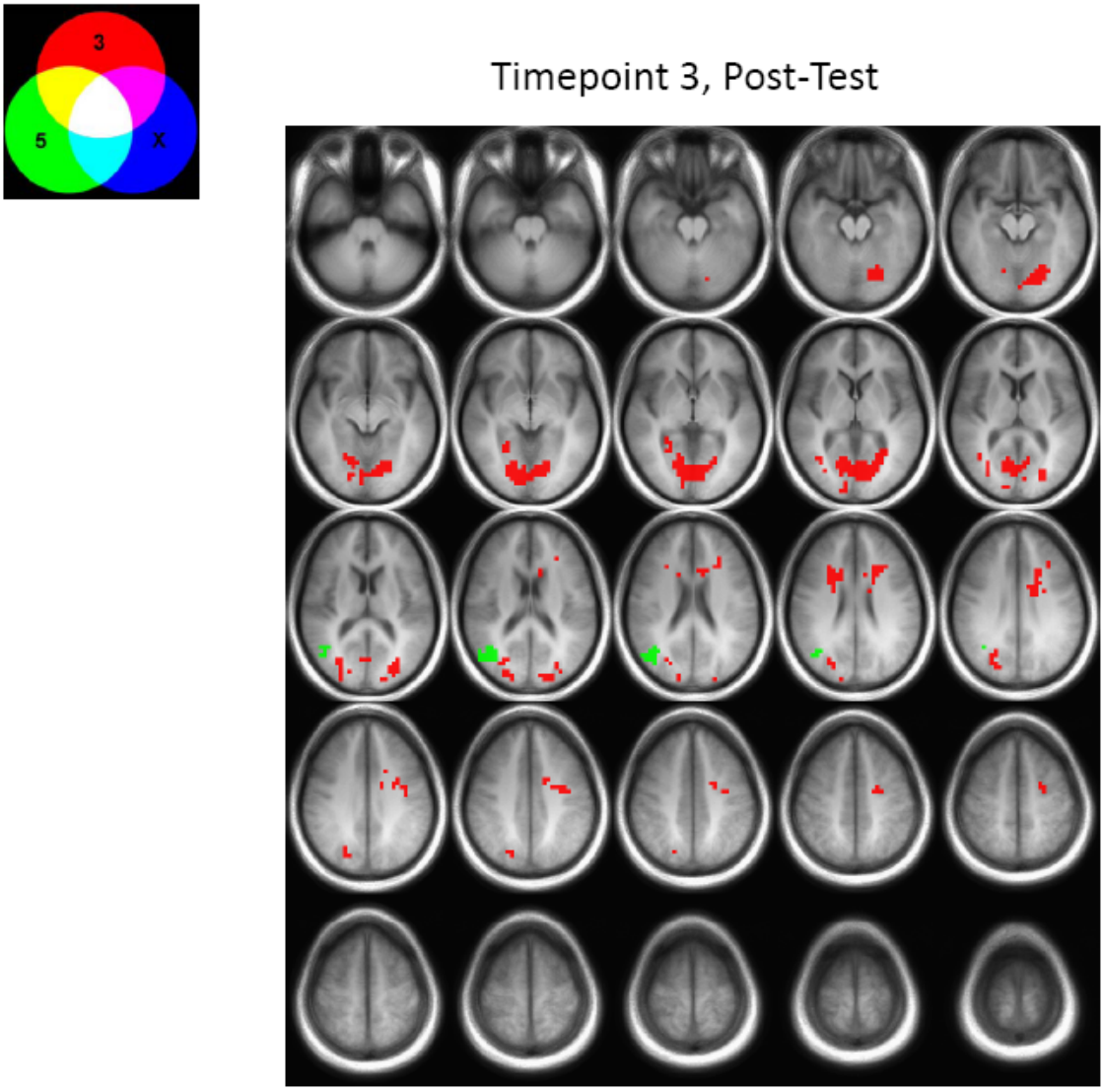
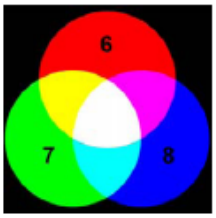


Figure 4.82 Mid-Test Components Analysis at Post-Test. Shown for all subjects at Post-Test.



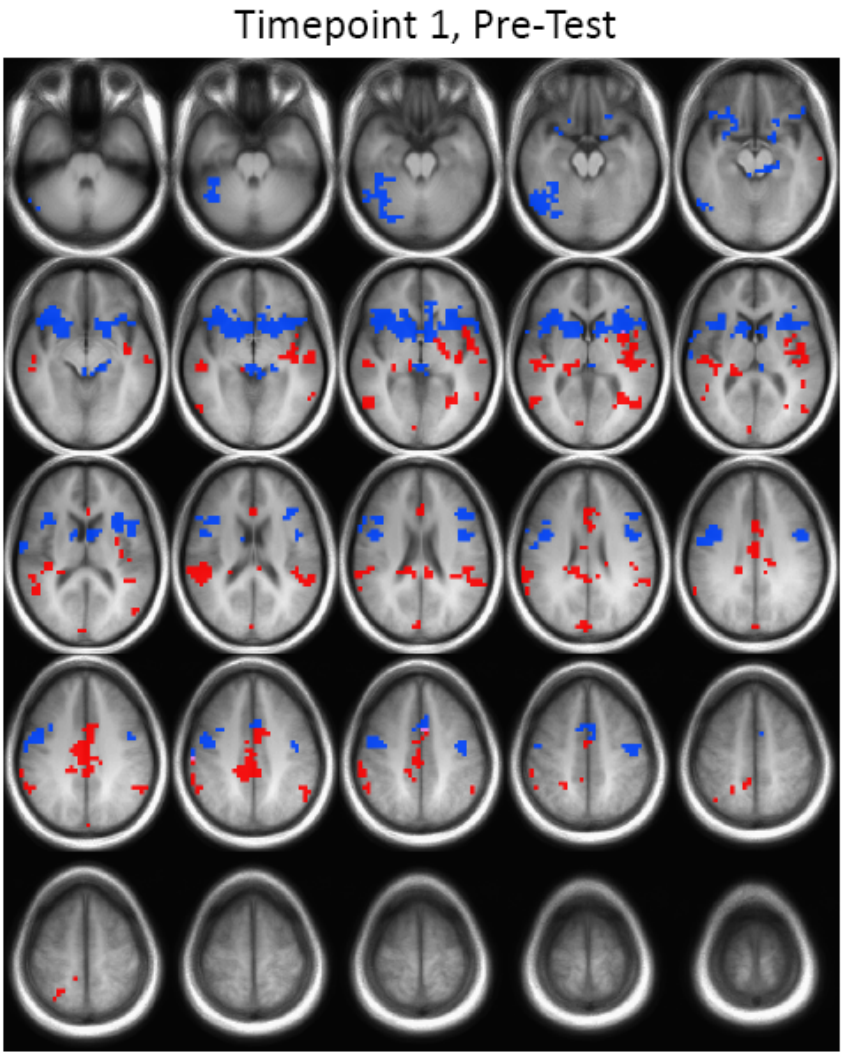
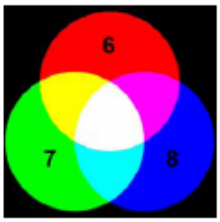


Figure 4.83 Post-Test Components Analysis at Pre-Test. Shown for all subjects at Pre-Test.



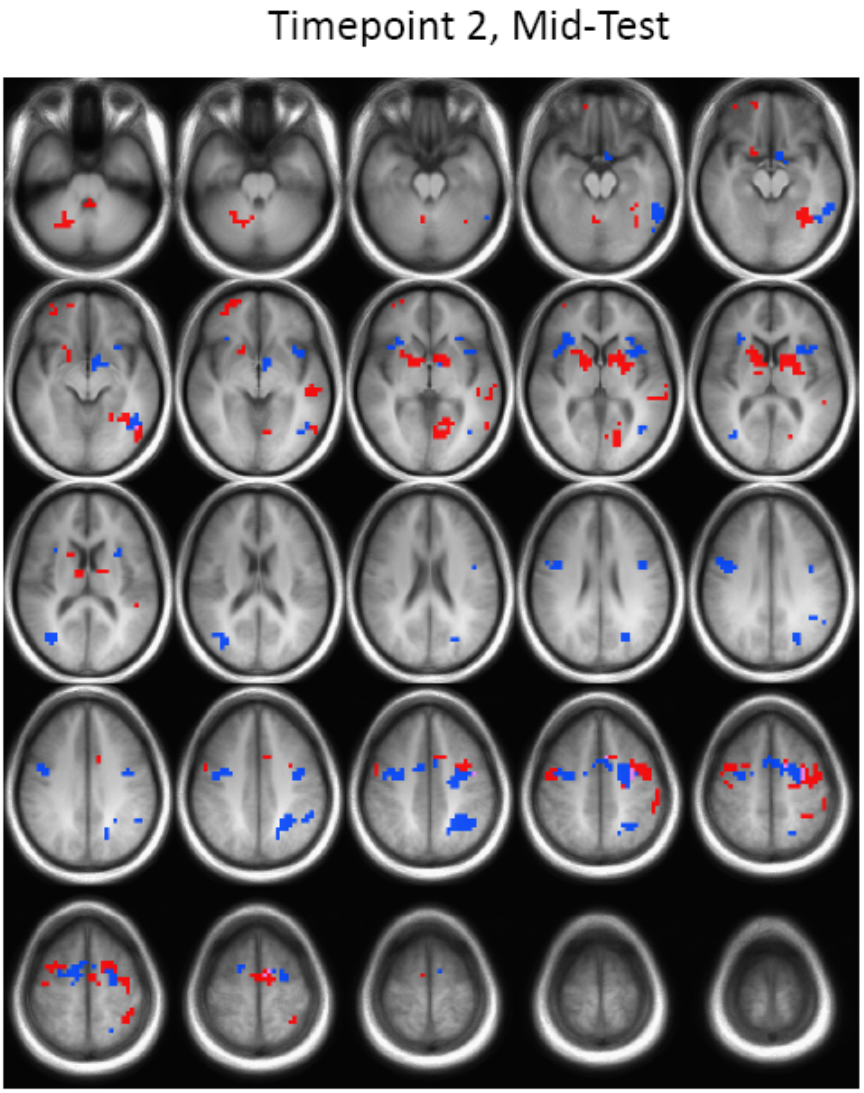


Figure 4.84 Post-Test Components Analysis at Mid-Test. Shown for all subjects at Mid-Test.

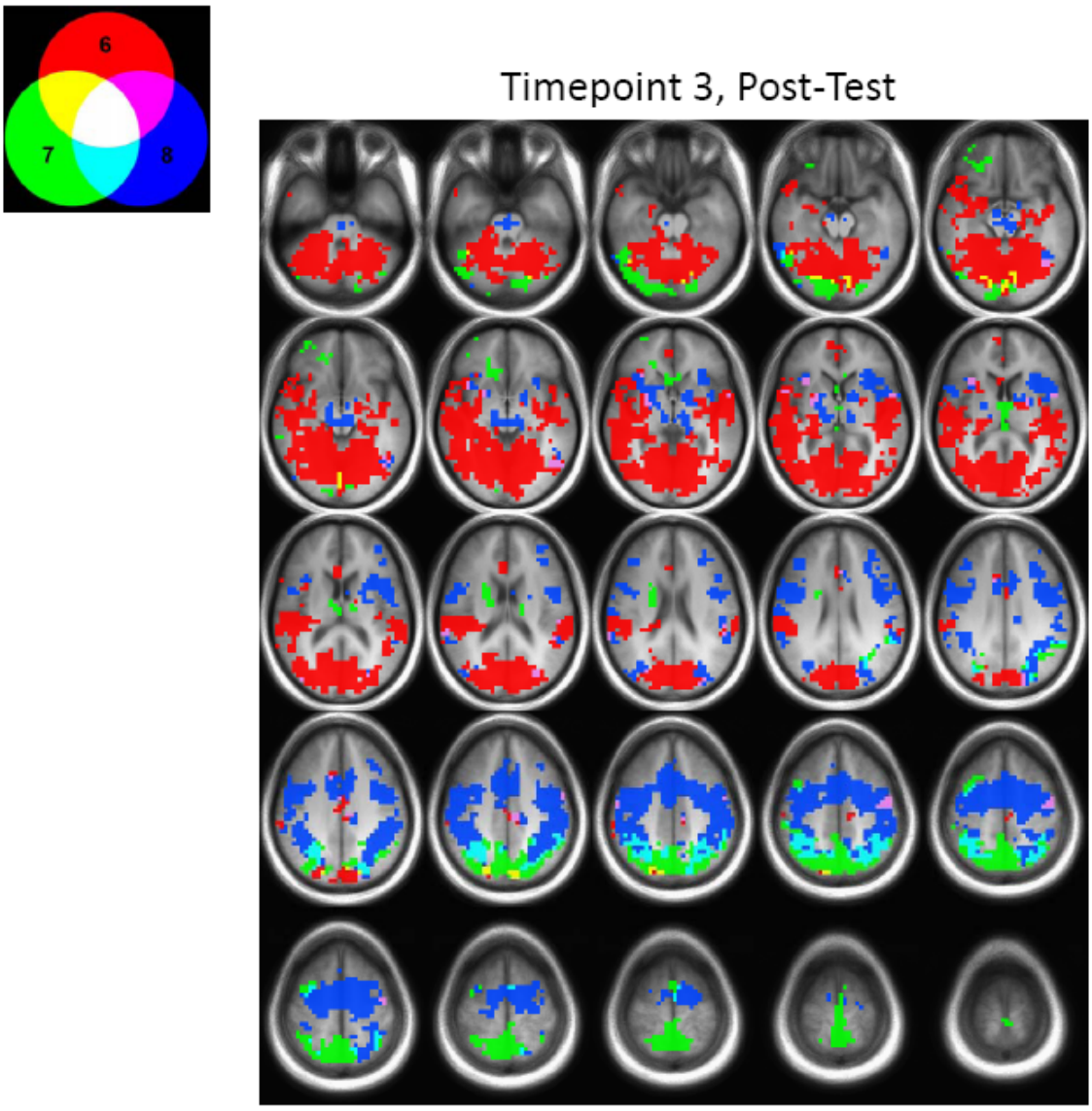


Figure 4.85 Post-Test Components Analysis at Post-Test. Shown for all subjects at Post-Test.

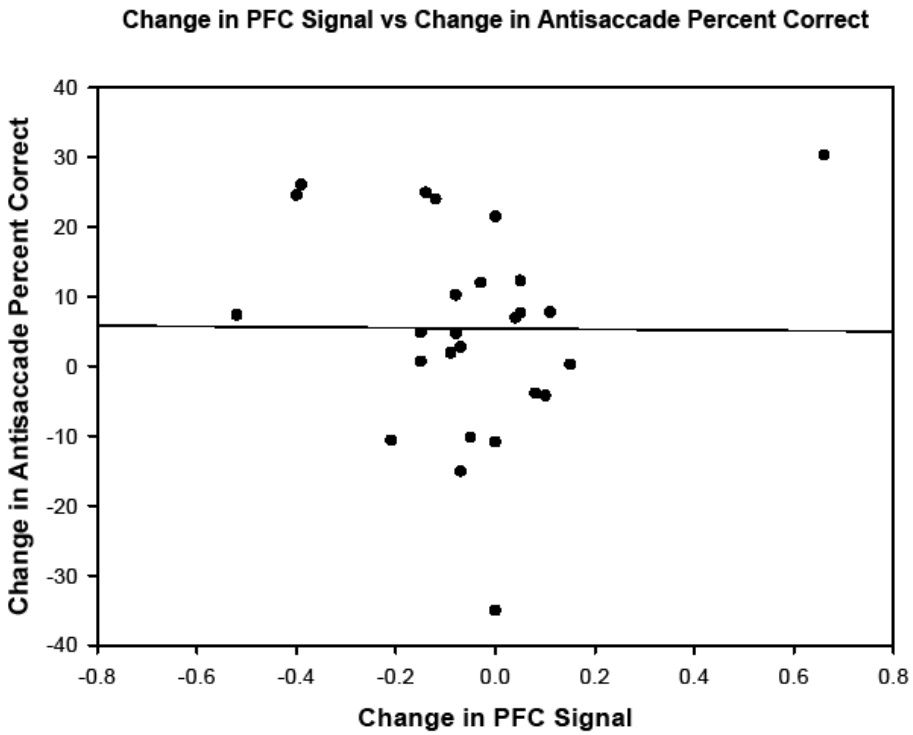


Figure 4.86 PFC vs Antisaccade Percent Correct. Shown for all schizophrenia participants. The change in PFC activity from pre-test to post-test demonstrates a nearly zero correlation with change in test-session antisaccade performance from pre-test to post-test ($r = +0.038$, $p = 0.859$), signifying that as PFC activity increases, antisaccade scores do not change.

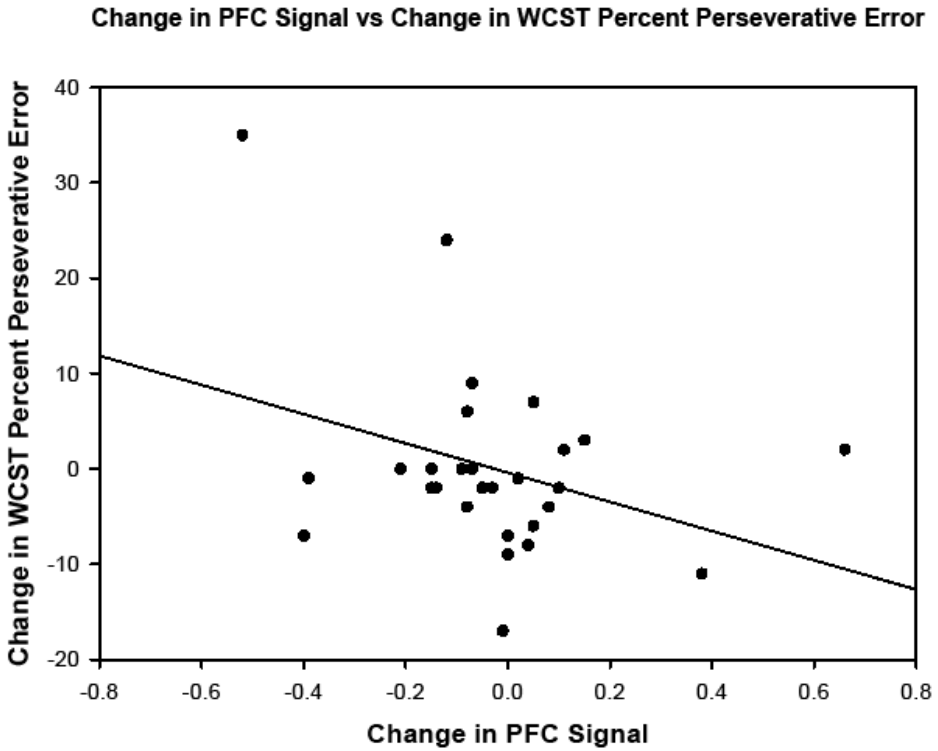


Figure 4.87 PFC vs WCST Perseverative Errors. Shown for all schizophrenia participants. The change in PFC activity from pre-test to post-test is moderately negatively correlated with change in WCST percent perseverative errors from pre-test to post-test ($r = -0.337$, $p = 0.079$), signifying that as PFC activity increases, perseverative error rates decrease.

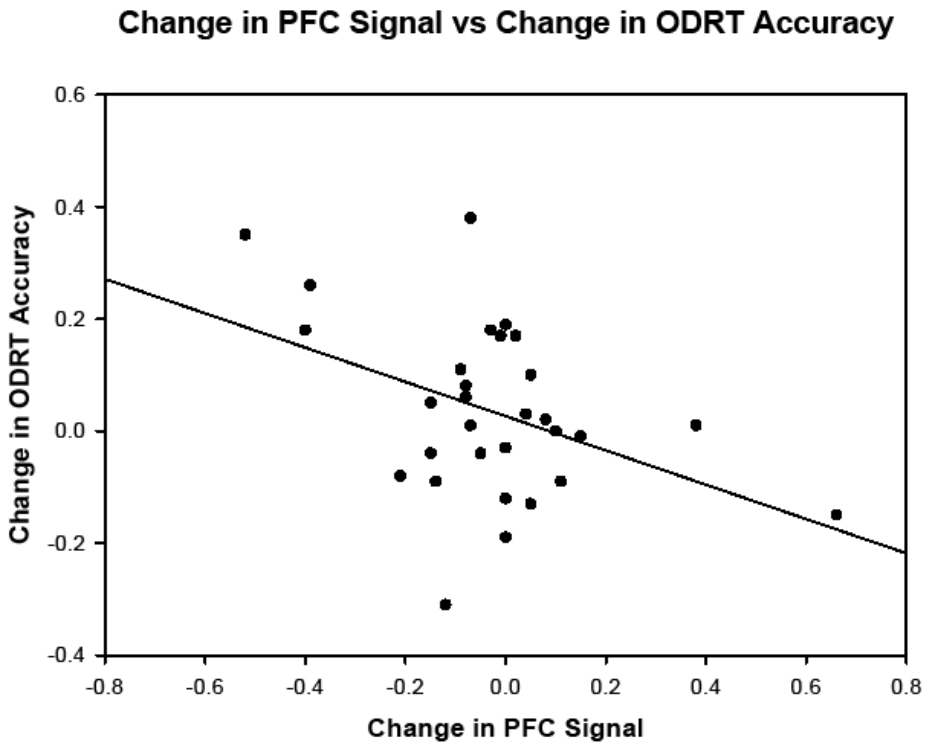


Figure 4.88 PFC vs ODRT Accuracy. Shown for all schizophrenia participants. The change in PFC activity from pre-test to post-test is significantly negatively correlated with change in ODRT accuracy of correct responses from pre-test to post-test ($r = -0.431$, $p = 0.022$), signifying that as PFC activity increases, accuracy decreases.

CHAPTER 5

DISCUSSION

In the current study 55 subjects participated in a 2-week trial. Pro- and anti-saccade performance was tested in the fMRI environment at three time points (Pre-, Mid-, and Post-Test). Between tests, participants engaged in daily practice of either pro- *or* anti-saccade tasks. FMRI BOLD data was analyzed across the three time-points, and eye movement data was evaluated for all fMRI and behavioral testing sessions. Pre- and Post-Test measures of executive functioning were assessed by ODRT and WCST. These data provide numerous comparisons, but those of greatest interest are grouped below into two main specific aims.

Specific Aim 1

The current study investigated whether among schizophrenia participants, behavioral performance following practice would show patterns similar to that documented in normal participants.

Hypothesis 1a

The first hypothesis stated that schizophrenia participants who practiced prosaccades would show decreased prosaccade latencies across time. Data from practice sessions for prosaccade practicers showed no significant main effect of time, although

there was a main effect of diagnosis, demonstrated as faster reaction times for the normal prosaccade practice group. Although the normal prosaccade practice group and the schizophrenia prosaccade practice group both showed a trend for decreasing latency over time, only the normal group showed a significant effect of time, a finding supported by previous studies of practice in normals (Fischer & Ramsperger, 1986).

For the test-session data, normal prosaccade practicers showed a trend for decreasing prosaccade latencies over time, which is similar to practice session data. The change was significant from pre-test to mid-test and from pre-test to post (but not mid-test to post-test) for both the prosaccade-fixation and antisaccade-prosaccade paradigms. For the schizophrenia group, however, the trend was irregular. For both the prosaccade-fixation and antisaccade-prosaccade paradigms, results show an increase in latency at mid-test and a decrease in latency at post-test, though none of these changes were significant.

For percent correct of prosaccades during practice sessions, analyses revealed that there were no significant effects of time, diagnosis, nor a time by diagnosis interaction. This is likely due to a ceiling effect, as both the normal and schizophrenia prosaccade practice groups performed near 100% at nearly every timepoint. It should be noted, however, that the schizophrenia prosaccade practicers appeared to have improved performance from session 1 to session 2, but the change was not significant.

For percent correct of prosaccades during test sessions, there was a significant interaction between time, diagnosis, and practice group. Post-hoc tests confirmed a difference between pro- and anti-saccade practicers at post-test (demonstrated as better performance in the prosaccade practice group), but no differences at mid-test or post-test.

There was a significant practice group difference in the schizophrenia group at post-test, demonstrated as higher numbers of correct responses in the schizophrenia prosaccade practice group compared to the schizophrenia antisaccade practice group, but there were no such differences at pre-test or mid-test. For the normal group, there were no significant differences between practice groups at any of the time points. Interestingly, post-hoc analyses revealed a significant decrease in performance for all subjects between pre-test and post-test, which was evident by marginally significant effects in both the normal and schizophrenia group.

In sum, trend-level data from practice sessions, supports the hypothesis that schizophrenia participants showed decreased prosaccade latencies across time, similar to normal participants who practice prosaccades. Test-session data show significant effects of decreasing latency for the normal prosaccade practice group between pre-test and mid-test and between pre-test and post-test, but no such effects are evident in the schizophrenia prosaccade practice group. For percent of correct prosaccade trials, practice session data show a ceiling effect for both groups, which supports the idea that the groups behave similarly, but test-session data are unclear.

Hypothesis 1b

The second hypothesis (Hypothesis 1b) stated that schizophrenia participants who practice antisaccades would show decreased antisaccade errors over time. Data from practice sessions for antisaccade practicers showed no significant effect of time nor a time by diagnosis interaction, however, a marginally significant effect of diagnosis suggests overall higher scores in the normal group compared to the schizophrenia group,

a finding supported by numerous studies (Fukushima, et al., 1994; Katsanis, et al., 1997; G. K. Thaker, et al., 2000). While the normal group appears to maintain percentage of antisaccade errors over time, the schizophrenia group shows a slight trend for improved performance over time, though the effect is not significant.

For test-session data, neither the schizophrenia nor normal antisaccade practice groups showed a significant effect of time. It should be noted, however, that during the antisaccade-fixation run, both antisaccade practice groups show a slight trend for improved performance, especially at mid-test, but during the antisaccade-prosaccade run, only the schizophrenia prosaccade practicers demonstrate this slight trend which continues through post-test. Post-hoc tests revealed that there were no significant changes between the three timepoints for either group for either paradigm.

Analyses investigating a possible speed accuracy tradeoff (increased latencies in favor of increased performance) revealed significant results during the practice sessions. Collapsing over all eight practice sessions, both the normal and schizophrenia antisaccade practice groups showed significant positive correlations between antisaccade percent correct and latency. For the schizophrenia group, significant correlations were evident at single timepoints (session 2 and 6, marginal significance at session 4 and 7), but for the normal group, there were no significant correlations at single sessions.

For the test-session data, there was a significant positive association between antisaccade performance and antisaccade latency for the schizophrenia group at mid-test, but there were no other significant speed accuracy tradeoff correlations at either pre-test, mid-test, or post-test for either all subjects, the normal group, the schizophrenia group, the prosaccade practice group, or the antisaccade practice group. Further analyses,

however, revealed differences between the four groups. The normal antisaccade practice group demonstrated week to moderate positive correlations during all three sessions (non-significant), while the normal prosaccade practicers demonstrated weak to moderate negative correlations during all three sessions (non-significant). The schizophrenia antisaccade group demonstrated strong positive correlations at pre-test and mid-test and a week (nearly zero) negative correlation at post-test, while the schizophrenia prosaccade group demonstrated a strong positive correlation at pre-test, a moderate positive correlation at mid-test, and a weak negative correlation at post-test.

In sum, it appears that schizophrenia participants who practice antisaccades are improving performance over time, if only at the trend-level. Trends for improved performance in the schizophrenia antisaccade practice group are shown over time in the practice data as well as test-session data, in which the change is most noticeable from pre-test to mid-test. The increase in antisaccade performance is evident in analyses of speed/accuracy trade off which is indicative of changed strategies. This is shown in both the practice session data (for all sessions and at single sessions 2, 4, 6, and 7) as well as the test-session data (strong positive correlations at pre-test and mid-test). Interestingly, the normal antisaccade practice group appears to demonstrate generally stable antisaccade performance throughout practice sessions, with only a slight trend for improved performance during test-sessions (increased antisaccade scores at mid-test for the antisaccade-fixation paradigm, but not for the antisaccade-prosaccade paradigm). It should also be noted that although the normal antisaccade practice group showed a significant speed/accuracy correlations for practice data collapsed across all sessions, this group, unlike the schizophrenia antisaccade practice group, failed to demonstrate

significant correlations at any single time-point. Also, while the normal group demonstrated positive speed/accuracy correlations at all three test sessions, none were significant, which is in stark contrast to the highly significant positive correlations for the schizophrenia antisaccade practice group at pre-test and mid-test.

Hypothesis 1c

The third hypothesis (Hypothesis 1c) stated that schizophrenia (like normal) participants would make more antisaccade errors following prosaccade practice, and they may be more susceptible to this manipulation than normal participants. For this evaluation of task-inconsistent practice, practice data cannot be used because participants are never exposed to the non-practiced trial types (i.e., prosaccade practice participants never experience antisaccade tasks in the laboratory). Thus the analysis will focus on data from test sessions.

Data from test sessions for antisaccade performance (combined from the antisaccade-fixation and antisaccade-prosaccade paradigm) revealed a significant time by diagnosis interaction in which normal participants demonstrated better antisaccade performance than schizophrenia participants at pre-test and mid-test, but not at post-test. Our finding that the schizophrenia group demonstrated performance deficits during antisaccades is supported by numerous studies in the literature (e.g., Calkins, et al., 2003; Curtis, et al., 2001; Ettinger, et al., 2004; Ettinger, et al., 2006; Karoumi, et al., 2001; Katsanis, et al., 1997; McDowell, et al., 1999; Radant, et al., 2007; Ross, et al., 1998). In the normal group, there was a significant improvement in antisaccade performance only from mid-test to post-test, and in the schizophrenia group, there was a significant

improvement in antisaccade performance only from pre-test to post-test. There was also a significant effect of practice group in which prosaccade practicers demonstrated better performance than antisaccade practicers. Data for antisaccade performance from the antisaccade-fixation paradigm revealed a marginally significant effect of practice group, shown again as greater percentage correct for the prosaccade group compared to the antisaccade group. Data for antisaccade performance from the antisaccade-prosaccade paradigm revealed a significant time by diagnosis interaction in which normal participants demonstrated better antisaccade performance at pre-test (significant) and mid-test (marginally significant), but not at post-test. In the normal group, there was a significant improvement in antisaccade performance only from pre-test to post-test, and in the schizophrenia group, there was also a significant improvement in antisaccade performance only from pre-test to post-test.

Further analyses investigated changes in performance for the normal and schizophrenia prosaccade practice groups. The normal prosaccade practice group showed differential patterns over time for the antisaccade-fixation and antisaccade-prosaccade paradigms. For both paradigms, there was a significant effect of time, however, the pattern of change for the antisaccade-fixation paradigm was a significant increase in performance from pre-test to mid-test and a significant decrease in performance from mid-test to post-test, whereas in the antisaccade-prosaccade paradigm, we see a increasing performance over the three sessions, which is significant from pre-test to post-test and from mid-test to post-test. For the schizophrenia prosaccade practicers, we see a more similar pattern between the antisaccade-fixation and antisaccade-prosaccade paradigms. This group appears to increase antisaccade

performance over the three timepoints for both paradigms, and though the effect of time is not significant for either paradigm, there is a significant difference between pre- and post-test scores for the antisaccade-fixation paradigm.

The changes in antisaccade performance for the normal and schizophrenia prosaccade practice groups were accompanied by changes in latency. During both the antisaccade-fixation paradigm and the antisaccade-prosaccade paradigms, the normal group showed a significant effect of time, demonstrated as a decrease antisaccade latency over the three sessions. For both paradigms, significant decreases in latency are reported from pre-test to mid-test and from pre-test to post-test, but not for pre-test to mid-test. The pattern of change in latency for the schizophrenia prosaccade practice group, however, differed between paradigms. In the antisaccade-fixation paradigm, the schizophrenia appeared to demonstrate consistent latency over the three time points, and there were no significant differences between any two timepoints. In the antisaccade-prosaccade paradigm, however, there was a significant decrease in antisaccade latency from pre-test to post-test, but not from pre- to mid-test or from mid- to post-test.

For antisaccade practicers it was hypothesized that prosaccade latencies may suffer during test sessions, however, this was not the case. For both the normal and schizophrenia antisaccade practice groups, there was no effect of time for either the prosaccade-fixation or antisaccade-prosaccade paradigm, and there were no significant changes between any two timepoints.

In sum, results suggest that neither schizophrenia nor normal participants make more antisaccade errors following prosaccade practice. In fact, the only instance of significant decrease in antisaccade performance was by the normal prosaccade practice

group during the antisaccade-fixation task from mid-test to post-test, a finding which only partially supports a previous study from our laboratory (Dyckman & McDowell, 2005). This group actually increased antisaccade performance from pre-test to mid-test during the antisaccade-fixation paradigm, and for the antisaccade-prosaccade prosaccade paradigm, increased antisaccade percent correct scores from pre-test to post-test and from mid-test to post-test. The improvements in antisaccade performance for the normal prosaccade practice group were accompanied by significant decreases in latency from pre-test to mid-test and pre-test to post-test for both paradigms. For the schizophrenia prosaccade practice group, we also see a trend for increasing antisaccade performance over time for both paradigms, though the effect of was not significant, except for pre- to post-test scores during the antisaccade-fixation paradigm. These changes in performance were accompanied by generally consistent antisaccade latencies over time for the antisaccade-fixation paradigm and decrease in antisaccade latency from pre-test to post-test during the antisaccade-prosaccade paradigm. Interestingly, antisaccade practicers did not demonstrate similar effects during their non-practiced tasks at test sessions; for both antisaccade practice group, there was no effect of time on prosaccade latencies for either paradigm, and no significant differences between any two timepoints.

Specific Aim 2

The second aim of the current study was to determine whether antisaccade-practiced schizophrenia participants would demonstrate a divergence from normal patterns of brain activity that is accentuated across time and that is related to both

antisaccade task performance and to executive function (as measured by ODRT and WCST).

Hypothesis 2a

The first hypothesis stated that schizophrenia and normal participants would show dissimilar patterns of brain activity change associated with antisaccade performance across time. At pre-test, it was expected that all participants would show activity in basic saccade-related regions (e.g. FEF, SEF, PPC) but that schizophrenia participants would show a dampening of signal particularly apparent in striatum (Raemaekers, et al., 2002) and PFC (McDowell, et al., 2002). ROI analyses confirmed that all subjects demonstrated activity in regions supporting antisaccade performance. These regions included SEF and the following bilateral regions: lateral FEF, medial FEF, PFC, IFC, precuneus, cuneus, IPL, MOG, striatum, thalamus, IFG (BA44), insula, and cerebellum. ROI analyses of striatum confirm a significant effect of diagnosis, demonstrated as greater percent signal change in the normal group compared to the schizophrenia group. ROI analyses of PFC, however, did not reveal a significant effect of diagnosis and there were no significant differences in percent BOLD signal change between the normal and schizophrenia groups at either pre-test, mid-test, or post-test.

Based on a previous study from our laboratory (Dyckman & McDowell, manuscript in preparation), it was hypothesized that over the 2-week trial, normal participants would show a decrease in antisaccade-related PFC activity. Repeated measures ANOVA showed that for normal participants in the current study, activity in bilateral PFC did show a trend for decreased activity over time, but the effect was not

significant. The change, however, was marked by a marginally significant decrease in activity from pre-test to post-test, but no significant changes were found from pre-test to mid-test or mid-test to post-test. Further analyses revealed that for the normal antisaccade practice group, there was a non-significant trend for decreasing activity in bilateral PFC over time, and the change was only significant from pre-test to post-test. For the normal prosaccade practice group, there also was no significant effect of time, but there appears to be a slight increase in activity from pre-test to mid-test, followed by a decrease in activity at posttest.

It was also hypothesized that the normal and schizophrenia antisaccade practice groups would show a dissociation of PFC activity across time; the normal participants would show decreased PFC signal and schizophrenia participants would show increased PFC signal, or a reversal of hypofrontality. This was not the case for the current study. In fact, schizophrenia participants demonstrated a trend for decreasing PFC activity over time. Although the trend was not significant, similar trends are shown for both the schizophrenia prosaccade and antisaccade practice groups. It should be noted, however, that there were no significant changes between any two time points for either the schizophrenia group as a whole, the schizophrenia prosaccade group, or the schizophrenia antisaccade practice group. Interestingly, though, there was a marginally significant difference between the schizophrenia practice groups for PFC signal collapsed over time, demonstrated as lower signal in the antisaccade practice group.

In sum, during the antisaccade-fixation paradigm, all participants demonstrated activity in basic saccade-related regions. While schizophrenia participants showed a significant dampening of signal in striatum compared to the normal group, there was not

a significant difference for PFC activity overall or at any single timepoint. Similar to previous studies (right PFC, Dyckman et al., manuscript in preparation), normal participants show a trend for decreased PFC activity across time (particularly from pre-test to post-test), but the effect was not significant for either practice group. Most importantly, the expected reversal of hypofrontality was not evident in the schizophrenia group, in which both practice groups demonstrated weak trends for decreasing PFC activity across time.

Hypothesis 2b

The second hypothesis stated that schizophrenia participants who show the greatest PFC change between pre-test and post-test will show the greatest improvement in executive functioning, as measured by improved antisaccade error rates, improved spatial accuracy during ODRT and fewer perseverative errors during WCST.

For schizophrenia participants, analyses revealed only a weak correlation between change in PFC activity across time and change in antisaccade performance across time, however, performance variables from WCST and ODRT were more revealing. Analyses of WCST performance parameters revealed a marginally significant negative correlation between change in PFC activity and change in rate of perseverative errors, signifying improved performance at post-test. Change in rate of perseverative responses also demonstrated a marginally significant negative correlation with change in PFC activity. The following measures, although not significant, also showed improvement at post-test and further corroborate the evidence that increasing PFC activity leads to improved performance: number of trials administered, percentage of errors, percentage of

conceptual level responses, number of categories completed, and number of trials to complete the first category. The only measurement that possibly opposed improved performance over time was percent of non-perseverative errors, but it should be noted that this measure only increased in the presence of decreasing preservative errors.

Analyses of ODRT performance parameters revealed a highly significant negative correlation between change in PFC activity and change in accuracy of ODRT trials, signifying that increased PFC activity leads to decreased accuracy at post-test. Increased PFC activity also slightly correlated with decreased performance at post-test (not significant) for percentage correct of ODRT trials and slower reaction times for correct responses. Increased PFC, however, activity may have improved performance in other ways; analyses revealed a trend for decreasing anticipatory saccades at post-test.

In sum, it is interesting that while both schizophrenia practice groups showed trends for decreasing PFC activity over time, there was a subset which demonstrated increased activity over time and whose performance on WCST and ODRT improved at post-test. Results suggest that schizophrenia participants who demonstrate increased PFC activity from pre-test to post-test tend to commit fewer perseverative errors on WCST, show a trend for improved performance on six other WCST measurements, and also commit fewer anticipatory saccades during ODRT at post-test. It should be noted, however, that accuracy of ODRT saccades may have suffered in compensation for increased inhibitory performance (fewer anticipatory saccades) at post-test.

Conclusions

The goal of the current study was to investigate neural plasticity associated with daily practice of saccadic tasks among schizophrenia and normal participants. It was hypothesized that following practice, schizophrenia participants would demonstrate behavioral performance patterns similar to their normal counterparts. This was true during practice sessions, in which data from both groups showed a trend-level decrease in prosaccade latency over time and a ceiling-effect for prosaccade performance. For antisaccade practicers, however, the schizophrenia and normal groups may be differing in behavioral patterns. While the normal antisaccade practice group appears to generally maintain antisaccade performance over time, the schizophrenia antisaccade practice group demonstrates trends for increasing antisaccade performance over time during both practice- and test-sessions which are coupled with significant speed-accuracy tradeoff correlations indicative of changed strategies. While the effects of practice on the performance of non-practiced tasks were consistent between normal and schizophrenia groups, results challenge previous findings. During test-sessions, antisaccade practicers showed no effect of disrupted prosaccade latency, and prosaccade practicers actually demonstrated increased antisaccade performance between timepoints.

It was also hypothesized that antisaccade-practiced schizophrenia participants would demonstrate a divergence from normal patterns of brain activity across time, notably in PFC. This was not true for the current study, as both groups (in fact, all groups) showed trends for decreasing PFC activity across time. Interestingly though, there exists a small subset of schizophrenia participants who do demonstrate increased PFC activity across time and whose reversal of hypofrontality is correlated with increased

performance on seven out of eight WCST performance measurements. Further studies are required to determine whether the improvement in generalized executive control for this small subset of patients will continue to respond positively to practice, and more importantly, whether improved executive function will sustain after practice trials.

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