FMRI/EEG STUDY OF CHANGES IN BEHAVIOR AND BRAIN ACTIVITY DURING AND AFTER SACCADE PRACTICE

by

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(Under the Direction of Jennifer E. McDowell)

ABSTRACT

Practice can lead to better performance of a task and changes in the neural circuitry underlying task performance. The present study used EEG and fMRI to examine changes in brain activity before, during, and after practice of saccade tasks. Thirty-two participants performed pro- and anti-saccade tasks in the fMRI scanner on the first day of the study. During daily practice sessions over a one-week period, EEG data were recorded as half of the participants practiced the prosaccade task and the other half practiced the antisaccade task. FMRI data were recorded at the end of the practice sessions.

Participants who practiced the prosaccade task generated saccades with faster latencies as well as an increased proportion of express saccades. Participants who practiced the antisaccade task had decreased latencies to correct antisaccades and showed improvement in the percent of correct antisaccades in the practice sessions. While many regions of the saccade circuitry remained stable across time, there were regions that showed decreased activity after practice. Right DLPFC, inferior frontal cortex, and cuneus showed decreased antisaccade-related activity at the second test session, regardless of practice group. Precuneus, inferior parietal lobule, and anterior cingulate cortex showed decreased antisaccade-related activity after antisaccade practice only, suggesting that practice results in increased efficiency within the circuitry.

Changes were also evident across EEG practice sessions. The prosaccade practice group showed increased preparatory period activity in parietal cortex across sessions, which corresponded to an increase in the proportion of express saccades generated. The antisaccade practice group showed decreased activity in right visual cortex approximately 100ms after stimulus presentation across sessions, which may be associated with top-down modulation of visual cortex to facilitate looking away from the peripheral stimulus.

The behavioral and brain imaging techniques used in the current study complemented each other to yield information about how practicing saccade tasks can affect the performance of saccades and the neural circuitry supporting these tasks. Results suggest that changes in brain activity after practice of saccade tasks reflect both (1) decreased reliance on regions supporting cognitive control and (2) increased efficiency in the neural circuitry specific to saccade tasks.

INDEX WORDS: Saccade, Practice effects, Antisaccade, Prosaccade, fMRI, EEG

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DEDICATION

This dissertation is dedicated to the memory of my father, Dr. Raul M. Abad, who showed me my first picture of the brain when I was just five years old.

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CHAPTER 1

INTRODUCTION

When a novel behavior is performed or a new skill is learned, accurate performance requires cognitive control, yet a well-practiced behavior or skill can be performed with very little effort. Cognitive control is the ability to guide behavior based on internal states or goals, such as selecting a weaker response that is consistent with task instructions, in the face of a more salient, but task-irrelevant alternative (e.g. Miller & Cohen, 2001). With practice, a task becomes more automatic, resulting in a reduced need for cognitive control and often, better performance of the task (e.g. Jansma et al., 2001; Schneider & Chein, 2003; Schneider & Shiffrin, 1977). Modifications in the neural circuitry underlying task performance have also been observed following practice (e.g. see Kelly & Garavan, 2005 for a review). These changes in brain activity likely include general changes reflecting a decreased need for cognitive control, as well as changes in the specific neural circuitry supporting the task of interest.

In the present study, changes in brain activity were examined before, during, and after practice of saccade tasks. Saccades are rapid shifts of gaze used to bring objects or locations into focus. These eye movements provide a specific, well-studied system within which to assess plasticity for a number of reasons. First, saccade types differ in the amount of cognitive control necessary for performance. Some saccades, such as prosaccades are more reflexive in nature and require little, if any, cognitive control. For the prosaccade task, participants must simply redirect their gaze to a newly appearing visual stimulus. Other types of saccades, such as antisaccades, are more complex and require cognitive control for correct performance. The antisaccade task requires a redirection of gaze to the *mirror image* location of the newly appearing visual stimulus. During this task, participants must inhibit the prepotent response to look at the stimulus, and instead, make a voluntary eye movement to a blank area of the screen. Thus, the antisaccade can be used to test predictions regarding voluntary behavior.

Second, in the absence of saccade practice, reaction time (Ettinger et al., 2003; Harris et al., 2006; Klein & Berg, 2001; Raemaekers et al., 2007; Roy-Byrne et al., 1995) and error rate on pro- and anti-saccades appear to be stable across time (e.g. Dyckman & McDowell, 2005; Harris et al., 2006; Klein & Berg, 2001; Raemaekers et al., 2007; Roy-Byrne et al., 1995). With practice, however, performance on pro-saccades (Dyckman & McDowell, 2005; Fischer & Ramsperger, 1986) and anti-saccades (Dyckman & McDowell, 2005; Fischer & Hartnegg, 2000) can improve.

Finally, the neural circuitry underlying saccadic eye movements is relatively well understood (e.g. Leigh & Zee, 1999; Pierrot-Deseilligny et al., 2003; Schall et al., 2002), providing a solid foundation for understanding changes in brain activity associated with practice. A network of subcortical and cortical regions involved in saccade generation has been identified through animal neurophysiology (e.g. Amador, et al., 2004; Bruce et al., 1985; Everling et al., 1999; Everling & Munoz, 2000; Funahashi et al., 1993; Schlag-Rey et al., 1997; Zhang & Barash, 2000), human lesion (e.g. Gaymard, et al., 1998; Pierrot-Deseilligny et al., 1991; Pierrot-Deseilligny et al., 2002), and neuroimaging studies (e.g. Brown et al., 2006; Connolly et al., 2002; Curtis & D'Esposito, 2003b; DeSouza et al., 2003; Dyckman et al., 2007; Ford et al., 2005; Matsuda et al., 2004; McDowell et al., 2002; Muri et al., 1998; O'Driscoll et al., 1995; Paus, 1996; Raemaekers et al., 2002; Sweeney et al., 1996). This circuitry will be discussed in detail in the following section.

The present study was designed to evaluate the plasticity of the neural circuitry supporting saccadic eye movements as responses become more practiced. All participants performed pro- and anti-saccade tasks in the fMRI scanner on the first day of the study, which provided a baseline level of activation in brain regions associated with saccades. After the initial fMRI session, half of the participants practiced the prosaccade task for one week, while the other half practiced the antisaccade task. EEG data were collected for each participant while they practiced their assigned task, and fMRI data were collected at the end of the practice period. This study extends the results of a previous fMRI study (Dyckman et al., in preparation); importantly, it differs from Dyckman et al. (in preparation) in several significant ways. First, the integration of fMRI and EEG data was used to provide optimal spatial and temporal resolution of brain activity (e.g. Garavan et al., 2002). This was the first study in our laboratory to combine the two technologies to investigate the same research question, and it is the first study to use FMRI and EEG to investigate functional neuroplasticity of the saccade system. The high spatial resolution of fMRI provides optimal detection of regions involved in saccade generation, and the collection of EEG data allows for the determination of whether saccade-related regions exhibit increased activity prior to or during response generation. Combining the strengths of these two complementary techniques will further our understanding of the functions of these brain regions during saccade tasks.

Second, recording brain activity and behavior throughout the practice period allows for the investigation of trends that would be missed if only pre- and post-practice sessions were evaluated. Length of practice, and the time at which participants are scanned can significantly affect the pattern of cortical plasticity observed (Kelly & Garavan, 2005). Thus, it is advantageous to measure brain activity on more than two occasions, so that a trend may be observed. FMRI or EEG data were collected on each day of the experiment, and thus, functional brain activity was recorded from completely naïve performance through highly practiced performance. The present study therefore yields a better understanding of the subtle changes that may occur as a new skill is acquired and becomes more automatic.

The goals of the study were as follows:

1. Replicate changes in saccade behavior with practice. Practice is expected to affect percent correct and reaction time on the antisaccade task, and the direction of behavioral change should be dependent upon the type of practice in which the participant engages, similar to Dyckman and McDowell (2005).
2. Investigate the spatial extent and intensity of activity in saccade-related brain regions, as measured by both fMRI and EEG, which should change as a result of practice. The direction of change should be dependent upon the type of task practiced (e.g. antisaccade or prosaccade).
3. Exploit the high temporal resolution of EEG to do the following:
    a. Eliminate incorrect trials from analysis.
    b. Examine preparatory activity present during the period prior to stimulus presentation.
    c. Separate trials to left and right stimuli. This allows for the investigation of occipital and parietal activity contralateral to where the stimulus is presented.

CHAPTER 2

LITERATURE REVIEW

The purpose of the present study is to investigate how practice affects performance and functional brain activity during pro- and anti-saccades. In order to make predictions about how daily training will lead to changes in performance and brain activity, it is necessary to review the literature on both saccades and practice effects. Thus, this literature review covers the following topics: behavioral characteristics of pro- and antisaccades, a description of the neural circuitry supporting saccade generation, the effect of practice on functional brain activity during other cognitive tasks, and specifically, a review of the handful of studies that have looked at the effect of practice on saccade tasks. Finally, a set of hypotheses for the current study is described.

Characteristics of Pro- and Anti-saccades

Saccadic eye movements are rapid shifts of gaze used to foveate objects or locations of interest. Their frequency in daily life and importance for complex tasks has resulted in an abundance of research delineating the characteristics of both basic and complex saccades. The prosaccade is a simple redirection of gaze to a newly appearing visual stimulus. The antisaccade task, on the other hand, requires participants to look to the *mirror image* location of the newly appearing stimulus, without first looking at it. Thus, it is a voluntary saccade during which participants must inhibit the prepotent response to look toward the stimulus and generate a saccade in the opposite direction. An initial glance toward the stimulus is considered a direction error.

The mechanism for correct antisaccade performance is not fully understood; however, recent models emphasize competition between exogenous (reflexive) and endogenous (voluntary) motor programs (Massen, 2004; Trappenberg et al., 2001). According to these models, a saccade is generated when neural activity surpasses a threshold. In the case of an antisaccade, two programs are initiated: a reflexive saccade toward the cue, and a voluntary saccade to the opposite side. The motor program that reaches threshold first will “win” the competition, and that saccade will be generated. These accumulator models are supported by neurophysiological evidence (Trappenberg et al., 2001) and behavioral experiments in which manipulating the speed of the endogenous component has predictable effects on antisaccade error rate and latency (Massen, 2004).

The latency of a saccade is the time from the onset of the peripheral stimulus to the initiation of the saccadic eye movement, which studies have operationally defined as the point at which the velocity of the eye movement exceeds 20-30 degrees/second (e.g Edelman et al., 2006; Fischer et al., 1997; Olk & Kingstone, 2003). Latency depends, in part, on when the fixation point is removed relative to the onset of the peripheral stimulus. If the fixation point is extinguished simultaneous with the appearance of the peripheral stimulus (regular), the average latency for a prosaccade has been reported as approximately 180ms (Fischer & Ramsperger, 1984), while the average latency for a correct antisaccade has been reported as approximately 250ms (Evdokimidis et al., 2002), although there is considerable variation in the literature. The antisaccade task requires additional time for the computation of the saccade vector, as the target location of the saccade is not the same as the stimulus location (Edelman et al., 2006; Olk & Kingstone, 2003). Inhibition of the prepotent response to look toward the cue also contributes to the longer latency of antisaccades relative to prosaccades (Edelman et al., 2006; Olk & Kingstone, 2003).

Removing the fixation point prior to the onset of the peripheral stimulus (gap) results in faster latency saccades (Fischer & Ramsperger, 1984). Gaps of 200ms have been shown to have the largest effect on latency for both pro- and anti-saccades (Fischer & Weber, 1997; Weber & Fischer, 1995). Prosaccades with a 200ms gap between fixation offset and peripheral cue onset average approximately 140ms (Fischer et al., 1993; Gezeck, et al., 1997). The gap period prior to target onset may allow for the disengagement of fixation and the subsequent build-up of neural activity in preparation for saccade generation. Thus, when the target appears, all processing has been completed aside from the calculation of the saccade metric (Fischer et al., 1993).

The introduction of a gap creates a separate peak in the prosaccade reaction time distribution. In the gap paradigm, there is generally a peak around 100ms, and another peak around 150ms (Fischer et al., 1993). The saccades around the first peak (90-135ms in humans) are called “express saccades”. Express saccades are considered reflex-like orienting movements (Fischer & Weber, 1997). In primates, it has been shown that express saccades are mediated through the retino-cortical-tectal pathway and can be generated in the absence of the frontal eye fields (Schiller et al., 1987), an important cortical region for saccade generation that will be discussed in the next section.

Reflex-like orienting would be detrimental during the antisaccade task, and as such, there are no “express antisaccades” (Fischer & Weber, 1997). When a gap is introduced in an antisaccade task, however, latencies are still reduced, reflecting the disengagement of fixation that was also observed for the gap prosaccade task (Fischer & Weber, 1992; 1997). Another characteristic of antisaccades affected by the time of fixation point offset is the percentage of direction errors. Participants make an increased percentage of direction errors on the gap version on the antisaccade task compared to the regular version of the task (Fischer & Weber, 1997; McDowell & Clementz, 1997).

The percentage of direction errors has been the most widely studied characteristic of antisaccades. It varies across the lifespan (Luna et al., 2001; Munoz et al., 1998; Olincy et al., 1997; Raemaekers et al., 2006b) and is increased in particular mental illnesses and neurological conditions (see Hutton & Ettinger, 2006, for a review). Children make an increased number of antisaccade errors, with error rate decreasing as age increases (e.g. Fischer et al., 1997; Fukushima et al., 2000). Young children (ages 5-8) make the greatest proportion of antisaccade errors (Munoz et al., 1998), but by the time of later adolescence (ages 15-17), error rate is similar to that of young adults (Luna et al., 2004; Munoz et al., 1998). Declines in antisaccade performance have also been observed in older adults (Olincy et al., 1997; Sweeney et al., 2001). Older adults tend to make increased antisaccade errors, and reaction times to correct antisaccades are longer (Olincy et al., 1997; Sweeney et al., 2001), which may be associated with changes in brain activity that occur during aging (Raemaekers et al., 2006b).

Increased error rates in patients with schizophrenia have been well established. Whereas the mean error rate for normal adults is approximately 20%, the mean error rate for patients with schizophrenia has been reported as anywhere from 25% to 70% (Hutton & Ettinger, 2006). Fukushima et al. (1988) were the first to observe that schizophrenia patients made more antisaccade errors than normal controls, and since then there have been over 40 studies yielding consistent findings (Hutton & Ettinger, 2006). Another consistent finding is that, although schizophrenia patients appear to be unable to inhibit the prepotent tendency to glance toward the stimulus, they subsequently correct their errors on the majority of trials, indicating that the patients are aware of where they are supposed to look. An increased proportion of errors on the antisaccade task has been observed in both medicated and unmedicated patients (Harris et al., 2006), as well as in the biological relatives of schizophrenia patients (e.g. Clementz et al., 1994; Curtis et al., 2001; Ettinger et al., 2004; Katsanis et al., 1997; McDowell et al., 1999), both of which suggest that increased errors are not due to medication effects or manifestation of the illness. Instead, poor antisaccade performance may be due to dysfunction of the basal-ganglia-thalamocortical circuitry (Camchong et al., 2006; Raemaekers et al., 2002).

Spatial accuracy, which is how close the saccade is to the intended spatial location, is another characteristic of pro- and anti-saccades that can be measured. Antisaccades tend to be more hypometric (undershoot the target) than prosaccades (Tatler & Hutton, 2006), which is partially explained by the fact that antisaccades are typically made to a location that lacks a visual target (Edelman et al., 2006). Although this saccade metric is among the least studied characteristics of saccades, there is evidence that patients with schizophrenia have reduced spatial accuracy to antisaccades compared to normal controls (e.g. Ettinger et al., 2004; Ross et al., 1998).

Saccades are especially good tasks for studying practice-associated changes because the previously mentioned characteristics of saccades appear to be stable over time. There are relatively few studies that have investigated the stability of saccades, however, they have been consistent in their findings that reaction times for both prosaccades and antisaccades are stable across test sessions (Ettinger et al., 2003; Harris et al., 2006; Klein & Berg, 2001; Raemaekers et al., 2007; Roy-Byrne et al., 1995). Evidence for the within subject stability of antisaccade direction errors is somewhat conflicting. Generally, test-retest correlations appear to be lower for percentage of antisaccade errors than for latency, but low numbers of errors may have led to a restriction of range that affected the correlations (Klein & Berg, 2001; Roy-Byrne et al., 1995). Ettinger et al. (2003) reported a significant decrease in errors from the first (20.9%) to the second (16.4%) test, and an increase in antisaccade spatial accuracy between test sessions, differences they attributed to practice effects; the first session served as practice for the second session. Two other studies, however, found no significant differences in antisaccade error rate between test sessions held one week (Raemaekers et al., 2007) and one year (Harris et al., 2006) apart.

Neural Circuitry Supporting Saccades

The well-defined neural circuitry underlying saccade generation provides a good baseline for detecting changes that may occur after practice. A network of subcortical and cortical regions involved in saccade generation has been identified through animal neurophysiology (e.g. Amador, Schlag-Rey, & Schlag, 2004; Bruce et al., 1985; Everling, Dorris, Klein, & Munoz, 1999; Everling & Munoz, 2000; Funahashi et al., 1993; Schlag-Rey et al., 1997; Zhang & Barash, 2000), human lesion (e.g. Gaymard, et al., 1998; Pierrot-Deseilligny et al., 1991; Pierrot-Deseilligny et al., 2002), and neuroimaging studies (e.g. DeSouza et al., 2003; Ford et al., 2005; McDowell et al., 2002; Muri et al., 1998; O'Driscoll et al., 1995; Paus, 1996; Raemaekers et al., 2002; Sweeney et al., 1996; Sweeney et al., 2007) (see Figure 2.1). At the subcortical level, the network includes the basal ganglia, thalamus, superior colliculus, and brainstem reticular formation (see Leigh & Kennard, 2004; Leigh & Zee, 1999; Wurtz & Goldberg, 1989). Cortically, this network includes the frontal eye fields (FEF), supplementary eye fields (SEF), and regions of posterior parietal cortex (PPC), as well as additional cortical regions, such as dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) that are recruited for more complex saccades (e.g. Brown et al., 2006; DeSouza et al., 2003; Ford et al., 2005; Matsuda et al., 2004; McDowell et al., 2002).

Generation of a saccade requires the innervation of the extraocular muscles by neurons in the brain stem. The neurons specifically important for the generation of horizontal saccades are burst neurons and omnipause neurons. Burst neurons in the paramedian pontine reticular formation (PPRF) can be either excitatory (EBN) or inhibitory (IBN). Excitatory burst neurons discharge immediately preceding a horizontal eye movement and are thought to generate the command for a horizontal saccade (Leigh & Zee, 1999). In contrast, the IBN prevent activity in the muscles responsible for a movement in the opposite direction of the intended horizontal eye movement. Omnipause neurons are located in the nucleus raphe interpositus and discharge on a continuous basis except during a saccade or a blink. In this way, omnipause cells inhibit burst cells, and therefore saccades, to keep the eyes stable during fixation. The brain stem saccadic pulse generators receive signals to generate a saccade from the superior colliculi and directly from frontal eye fields (FEF) located in the cortex, both of which receive signals from other cortical and subcortical regions within the saccade circuitry.

Visual Cortex

A visually guided saccade begins with the presentation of the visual stimulus. The visual information enters the system through the retina and travels through the lateral geniculate nucleus of the thalamus to visual cortex. The visual stimulus is registered in contralateral visual cortex beginning approximately 100-120ms after presentation (Clementz et al., 2007; McDowell et al., 2005; Tendolkar et al., 2005; Tzelepi et al., 2004). There is some evidence that visual cortex activity is stronger for prosaccades than for antisaccades (Dyckman et al., 2007; McDowell et al., 2005). In a combined EEG/MEG study, McDowell et al. (2005) observed greater activity in this region from the time of stimulus onset through 170ms post-stimulus, which may reflect top-down influences from frontal cortex; for the antisaccade task, participants are not supposed to look at the stimulus, and therefore, may invest fewer cortical resources in encoding the peripheral stimulus. From the visual cortex, the signal travels via the dorsal stream to posterior parietal cortex, specifically the intraparietal sulcus (IPS) in humans, which may correspond to the monkey parietal eye field located in lateral intraparietal area (LIP) (Medendorp et al., 2005).

Posterior Parietal Cortex

Posterior parietal cortex, specifically intraparietal sulcus, is important for the transformation of a sensory input into a motor command. Lesions to this area (Pierrot-Deseilligny et al., 2002) and transcranial magnetic stimulation (TMS) over the right posterior parietal cortex (Kapoula et al., 2001) result in increased latency to visually-guided saccades. Lesions also result in inaccurate saccadic gain (Gaymard et al., 1998), which is consistent with the role of this area in visuospatial integration (Matsuda et al., 2004) and shifts in attention (Leigh & Zee, 1999).

Evidence suggests regions in the area of intraparietal sulcus perform the vector inversion required to generate an antisaccade to the correct location (e.g. Clementz et al., 2007; Moon et al., 2007; Medendorp et al., 2005; Zhang & Barash, 2000). Zhang and Barash (2000) recorded from neurons in LIP in nonhuman primates while they performed pro- and anti-saccade tasks. They found that population activity in this region switched from encoding the stimulus location to encoding the motor direction within 50 ms after signals reached LIP (Zhang & Barash, 2000).

Consistent with the role of posterior parietal cortex in vector inversion, human neuroimaging studies have consistently found greater activity during the generation of antisaccades than during the generation of prosaccades (e.g. Curtis & D’Esposito, 2003b; DeSouza et al., 2003; Doricchi et al., 1997; Dyckman et al., 2007; Ford et al., 2005; Luna et al., 2001; Moon et al., 2007; Medendorp et al., 2005; Raemaekers et al., 2006a, 2006b). Studies employing methods with high temporal resolution allow for the observation of whether particular brain regions exhibit activity prior to or after response generation, and thus these studies can provide even more information about the putative roles of these regions. In an event-related fMRI study, Medendorp et al. (2005) found contralateral hemisphere activity in response to visual stimulus in an area they called retinotopic intraparietal sulcus (retIPS), which is situated similarly to the precuneus area identified in other studies (e.g. Dyckman et al., 2007). Once the instruction to make an antisaccade was given, however, activity shifted from the hemisphere contralateral to the visual stimulus to the hemisphere contralateral to the saccade goal. Thus, activation within retIPS seemed to code the spatial goal (Medendorp et al., 2005).

Using MEG, Moon et al. (2007) also found evidence that intraparietal sulcus is involved in vector inversion during antisaccades. Specifically in the left hemisphere, IPS showed early activity in response to the presentation of the stimulus in the contralateral visual field. Approximately 90ms later, however, this region showed activity contralateral to the intended location of the saccade. The same pattern of activity was also observed in FEF, suggesting that vector inversion may take place in IPS and send the signal downstream to FEF. Posterior parietal cortex also projects to other oculomotor areas within frontal cortex, such as supplementary eye fields (SEF), and dorsolateral prefrontal cortex (DLPFC).

Frontal Eye Fields

The FEF in humans are located in Brodmann area 6, in the precentral sulcus, anterior to the motor strip (Paus, 1996) and are associated with the initiation of voluntary saccades (e.g. Bruce & Goldberg, 1985; Rivaud et al., 1994; Pierrot-Deseilligny et al., 1991). The location in humans has largely been determined through neuroimaging studies, and it is more posterior to the location of FEF in monkeys (Paus, 1996), although the regions are similar in chemoarchitecture (Rosano et al., 2003). This region was defined in monkeys as the area in which electrical stimulation of less than 50uA elicited a saccade (Bruce & Goldberg, 1985). Using single-unit recording, activity in FEF was also shown to be correlated with saccade latency in monkeys (e.g. Dorris & Munoz 1998). The lower the pre-target activity in FEF, the longer it took to boost the firing rate past the threshold for saccade triggering. Thus, the amount of activity in FEF when the target is presented may partially account for variations in reaction time within individuals or across different saccade paradigms (i.e. regular vs. gap saccades).

Movement cells within the primate FEF show activity before intentional saccades; however these cells are not active prior to spontaneous saccades (Bruce & Goldberg, 1985). Consistent with the role of FEF in voluntary saccade generation, lesions to FEF lead to increased latencies to correct antisaccades and memory-guided saccades (Rivaud, et al., 1994), but do not affect latencies to reflexive visually-guided saccades (Pierrot-Deseilligny et al., 1991).

Similar to findings for PPC, human neuroimaging studies have consistently found greater activity for antisaccades than prosaccades (e.g. Clementz et al., 2007; Curtis & D’Esposito, 2003b; DeSouza et al., 2003; Doricchi et al., 1997; Dyckman et al., 2007; Ford et al., 2005; Luna et al., 2001; Manoach et al., 2007; McDowell et al., 2005; Raemaekers et al., 2006a, 2006b). Increased BOLD signal in FEF on anti- compared to pro-saccade trials has been observed prior to saccade generation (e.g. Clementz et al., 2007; Connolly et al., 2002; DeSouza et al., 2003; Ford et al., 2005; Manoach et al., 2007; McDowell et al., 2005), suggesting that FEFs are involved in the inhibition of the prepotent response necessary for correct performance of antisaccade tasks. This increase in FEF activity has been interpreted as a heightened level of inhibitory input to this region in preparation for an antisaccade (DeSouza et al., 2003; Manoach et al., 2007). The time course of FEF activity, particularly its medial aspect, prior to anti-saccade generation is consistent with this possibility (McDowell et al., 2005). Curtis and D'Esposito (2006) also found that FEF activity persisted after response selection until a saccade was made, suggesting that FEF are involved in prospective coding of the saccade goal.

As previously mentioned, FEF project directly to neurons within the reticular formation; they also have projections to the superior colliculus, as well as interconnections with SEF and DLPFC.

Supplementary Eye Fields

SEF is located on the dorsomedial surface of the hemisphere, anterior to the supplementary motor area (Leigh & Zee, 1999; Pierrot-Deseilligny et al., 2002), and it is thought to be the ocular motor extension of the supplementary motor area (Schall et al., 2002). The exact function of SEF in saccade generation is still under investigation, however, studies have indicated a role for SEF in cognitive control during saccade tasks, specifically during generation of complex saccades (Parton et al., 2007; Stuphorn et al., 2000). Lesions of SEF do not affect visually-guided saccades, but patients with SEF lesions may have difficulty performing memorized sequences of saccades (Gaymard, et al., 1998). A 55 year old patient with a highly focal lesion of SEF was tested recently on a number of saccade tasks to determine which oculomotor behaviors critically rely on an intact SEF (Parton et al., 2007). The most salient deficit Parton et al. (2007) observed was a difficulty in controlling response selection when faced with competing saccade plans. For example, when prosaccades and antisaccades were interleaved, the patient made significantly more prosaccade errors compared to when prosaccades were presented by themselves. Although the patient did not make more antisaccade errors than age-matched controls, his responses were slowed.

Increased activity during antisaccades relative to prosaccades has been observed in SEF in both single-unit recording studies (e.g. Amador et al., 2004; Schlag-Rey et al., 1997) and human neuroimaging studies (e.g. Clementz et al., 2007; Curtis & D'Esposito, 2003b; DeSouza et al., 2003; Doricchi et al., 1997; Dyckman et al., 2007; Ford et al., 2005; Luna et al., 2001; McDowell et al., 2005; O'Driscoll et al., 1995; Raemaekers et al., 2006a, 2006b). Schlag-Rey et al. (1997) found that SEF neurons fired more before anti- than before pro-saccades. Consistent with a competition model of saccade generation, they suggested that the signal to generate a voluntary anti-saccade competes with the signal to generate a reflexive glance toward the cue, and that it is this increased SEF neuron activity prior to anti-responses that offsets the tendency to glance toward the peripheral cue. In this way, SEF could slow the buildup of neuronal activity leading to a reflexive saccade (Boxer et al., 2006), allowing the initial saccade to be the anti-response, and/or strengthen fixation activity to the central stimulus (Amador et al., 2004; Curtis & D'Esposito, 2003b).

SEF is connected to many of the same regions as FEF, such as DLPFC and PPC, although it is most densely connected to FEF itself (Lynch & Tian, 2005). SEF also has reciprocal connections with pre-supplementary motor area (pre-SMA), and in fact may serve as an intermediary between pre-SMA and FEF (Miller et al., 2005).

Pre-Supplementary Motor Area

Recent studies have suggested that pre-SMA, which is located just rostral to SEF and the vertical plane of the anterior commisure, has distinct functional properties in saccade generation (e.g. Curtis & D'Esposito, 2003b; Merriam et al., 2001; Miller et al., 2005). Merriam et al. (2001) observed greater activity in this region during saccade tasks that required greater demand on attentional control. Consistent with this, Curtis and D'Esposito (2003b) found that during a delay period prior to stimulus onset, pre-SMA showed increased BOLD signal for antisaccades compared to prosaccades. They also observed greater activity in this region prior to correct antisaccades compared to error antisaccades. This was the only region in their study that showed such a pattern. Using the same dataset as Curtis and D'Esposito (2003b), Miller et al. (2005) examined functional connectivity for saccade tasks. Based on their results, they suggest that pre-SMA coordinates with FEF to maintain a preparatory set prior to the onset of the peripheral stimulus. This coordination may take place through SEF as both regions have strong reciprocal connections with SEF.

Dorsolateral Prefrontal Cortex

DLPFC is located on the dorsolateral surface of frontal lobe, including middle frontal gyrus and adjacent cortex (BA 9 & 46; Leigh and Zee, 1999), and has long been associated higher cognitive functions, such as attention, planning, spatial orientation, and behavioral restraint (Goldman-Rakic, 1987). Lesions to dorsolateral prefrontal cortex (DLPFC) do not result in changes to visually-guided saccade performance, however, patients with discrete lesions to DLPFC make an increased percentage of errors on the antisaccade task (Pierrot-Deseilligny et al., 1991; Pierrot-Deseilligny et al., 2003).

Several human neuroimaging studies have reported DLPFC activity exclusively during antisaccades, with no significant activity during prosaccades (e.g. DeSouza et al., 2003; Matsuda et al., 2004; McDowell et al., 2002; Muri et al., 1998; Sweeney et al., 1996). DeSouza et al. (2003) used an event-related fMRI design to examine cortical activity that occurred in preparation for and during the execution of correct antisaccades. Right DLPFC showed significantly greater activity during the instruction phase prior to the antisaccade task than during the same period prior to the prosaccade task. This increase in activity took place before the cue to generate the antisaccade was given and may reflect top-down control signals to inhibit the unwanted reflexive saccade. Ford et al. (2005) and McDowell et al. (2005) also found increased DLPFC activity prior to antisaccade generation, consistent with the putative role of DLPFC in the inhibition of an unwanted saccade toward the peripheral cue.

Not all studies have shown increased DLPFC activity during antisaccades relative to prosaccades (e.g. Kimmig et al., 2001; O'Driscoll et al., 1995; Paus et al., 1993; Raemaekers et al., 2002, 2006a, 2006b); however, the context in which the tasks are performed has been shown to affect the brain activity supporting pro- and anti-saccade tasks (Dyckman et al., 2007). In an fMRI study by Dyckman et al (2007), participants performed pro- and anti-saccades in single saccade runs (i.e. only prosaccades or only antisaccades) and in a mixed saccade run (i.e. blocks of prosaccades alternating with blocks of antisaccades). Activity in DLPFC was greater for antisaccades than prosaccades when the single saccade runs were compared to one another, but when the tasks were presented together, there was no differential activity in DLPFC. One possible explanation for why there were no activity differences between the tasks during the mixed saccade run in this study, and other studies with similar paradigms, is that this region may have exhibited tonic activity across the mixed saccade run, due to its increased difficulty and more complex response selection requirement.

Findings from an EEG study by Clementz et al. (2007) are consistent with this interpretation. Participants completed prosaccade trials, antisaccade trials, and no-go trials in an interleaved fashion. The high temporal resolution of EEG allowed for the distinction of several peaks of activity that would not have been evident using fMRI. Early right PFC activity (158ms post-stimulus presentation) was greater for antisaccade trials than for pro- or no-go trials, but later activity in this region (204ms post-stimulus) was the same for anti- and pro-trials. The lack of differences in PFC between between pro- and anti-trials at the later timepoint is consistent with a lack of differential PFC activity in mixed saccade runs (Dyckman et al., 2007). There was however, a significant negative correlation between activity in right PFC and contralateral middle occipital gyrus at this timepoint for the antisaccade trials only. Greater PFC activity was associated with reduced activity in middle occipital gyrus, perhaps exerting a top-down influence on visual cortex to suppress activity in order to avoid making a reflexive movement toward the stimulus.

Anterior Cingulate Cortex

The anterior cingulate cortex (ACC) is thought to be important for general conflict monitoring (e.g. MacDonald et al., 2000; Miller & Cohen, 2001), but studies have also suggested that ACC is specifically involved in antisaccade performance (e.g. Brown et al., 2006; Doricchi et al., 1997; Gaymard et al., 1998; Matsuda et al., 2004; Milea et al., 2004). Lesions to ACC that spare DLPFC result in the inability to inhibit reflexive saccades in the antisaccade task (Gaymard, et al., 1998; Milea et al., 2003). This finding is consistent with reports of increased ACC activity during other tasks requiring inhibitory control (e.g. Braver et al., 2001; Garavan et al., 2002), and suggests that the suppression of unwanted saccades involves the ACC

Recent studies have suggested that the ACC monitors performance and that activity in ACC signals an increased likelihood for error (Brown & Braver, 2005; Ford et al., 2005; Johnston et al., 2007). Ford et al. (2005) found increased activation of ACC for antisaccades, when an error is more likely, compared to prosaccades, when an error is less likely. Importantly, they also observed greater ACC activity for correct antisaccades as opposed to incorrect antisaccades in the period prior to stimulus onset, which suggests a role for ACC in top-down control. During the stimulus-response period, however, they observed greater ACC activity for incorrect antisaccades, suggesting a role for ACC in error monitoring. Anterior cingulate cortex is reciprocally connected to prefrontal cortex (Bates & Goldman-Rakic, 1993; Paus et al., 2001) and may send signals to prefrontal cortex to exert top-down control when performing tasks, like the antisaccade task, where an error is likely (Johnston et al., 2007).

Summary of Cortical Regions

When a visual stimulus is detected in visual cortex, the signal typically travels to parietal cortex, where the sensory command is transformed into a motor command. From parietal cortex, the signal is sent to the frontal regions of the oculomotor network, namely FEF, SEF, DLPFC, and ACC. Within the frontal network, decisions are made about whether a saccade is warranted, and if so, what type of saccade should be generated. Although the basic cortical circuitry is common to all types of saccades, neuroimaging and single-unit recording studies provide evidence that increased activity in this network is required for more complex saccades.

Basal Ganglia

The oculomotor regions in frontal cortex project to the superior colliculus and thalamus via two pathways through the basal ganglia. The basal ganglia are a group of subcortical structures associated with the control of movement. The basal ganglia can facilitate initiation of a voluntary saccade or aid in the inhibition of an unwanted saccade (Leigh & Zee, 1999). The caudate nucleus and putamen, collectively called the striatum, receive input from the cortex. From the striatum, the signal may travel through either the Direct or Indirect pathway. A signal traveling through the direct pathway disinhibits the superior colliculus and thalamus, and thus, these regions are able to send excitatory signals to the reticular formation for saccade generation or back to frontal cortex. A signal traveling through the indirect pathway, however, inhibits the superior colliculus and thalamus, and thus, no signal is sent to the reticular formation or back to frontal cortex.

Thalamus

Within the basal ganglia-thalamo-cortical circuitry, the thalamus sends projections back to frontal cortex. In addition to relaying information from subcortical to cortical regions of the oculomotor network, there is additional information processing that takes place in the thalamus, although the precise nature of the role of the thalamus in saccadic eye movements is not yet well understood (Lynch & Tian, 2005). After a saccade is executed, the thalamus receives information about the saccade from the superior colliculus. In a study by Sommer and Wurtz (2004) the thalamus received sensory and motor information from the superior colliculus, as well as information regarding the delay between the onset of the stimulus and the onset of the saccade. The FEF, however, received only the sensory and motor information from the thalamus, suggesting additional processing, including filtering of information, was taking place in the thalamus.

Superior Colliculus

The basal ganglia project to the ventral layers of the superior colliculi, which are the motor layers. Electrical stimulation of this region yields saccades of predictable size and direction depending on the point of stimulation (Leigh & Zee, 1999). As previously stated, projections sent via the direct pathway through the basal ganglia disinhibit the superior colliculus, and thus allow an excitatory signal to be sent to the PPRF to generate a saccade. Projections sent via the indirect pathway, however, inhibit the superior colliculus. No signal is sent to the PPRF and thus, no saccade is generated.

Stability of Functional Brain Activity Associated with Saccades

While neuroimaging has been used to investigate the neural correlates of saccades in numerous studies, only one published study to this point has investigated the stability of functional brain activity associated with saccades over time (Raemaekers et al., 2007). In the study by Raemaekers et al. (2007), 12 participants performed pro- and anti-saccade tasks in an fMRI environment. Two measures were used to determine the test-retest reliability of the BOLD signal during pro- and anti-saccades. The amount of overlap in activation in regions of interest between the two sessions was calculated for individual subjects as well as for the group-wise comparison, and intraclass correlations were computed for individual and group data. The amount of overlap for the group t-volumes for both pro- and anti-saccades was high, indicating good test-retest reliability for groups of this size. Individual reliability was not as strong; however, this was largely due to differences in individual signal-to-noise ratios (SNR) and not due to variable brain activation across sessions. In sum, group-wise t-maps were highly reliable with a group of 12 subjects, even with the reduced detection power of a sparse event-related design. With a blocked design, where detection power is greater, the reliability may be even better. The well-defined neural circuitry of saccades coupled with the reliability of functional brain activity associated with pro- and anti-saccades allows for the detection of changes in brain activity that may occur after practice.

The Effect of Practice on Functional Brain Activity

Functional MRI has been used in a number of recent studies to investigate changes in brain activity following practice (e.g. Hempel et al., 2004; Jansma et al., 2001; Kassubek et al., 2001; Landau et al., 2004; Poldrack et al., 2005, Weissman et al., 2002). Although there are three main patterns of activation changes that have been observed after practice (see Kelly &

Garavan, 2005 for a review), the pattern observed in a particular study largely depends on the type of task, the extent of practice, and the amount of time between imaging sessions. The first pattern, a decrease in activation in the same anatomical structures supporting the initial performance of the skill, is most often seen with the practice of higher cognitive tasks (see Chein & Schneider, 2005 for a review). This pattern suggests that practice of the task increases the efficiency of the neural circuitry (e.g. Jansma et al., 2001; Kassubek et al., 2001; Tomasi et al., 2004). The second pattern involves an increase in activation either by strengthening the activity in task-related areas or by expanding the cortical representation of the practiced task (Kelly & Garavan, 2005). This pattern of change is most often seen with the practice of motor tasks, and the increased activation is usually observed in primary motor or sensory cortices (e.g. Karni et al., 1995; Pantev et al., 1998). Finally, it is possible that once a task becomes well-practiced, a restructuring takes place whereby new cortical areas become responsible for performing the same task. This pattern was observed by Poldrack and Gabrieli (2001) after training participants to read mirror-reversed words. This functional reorganization after practice was attributed to a change in the proportion of time spent on each aspect of the tested task. After practice, participants spent less time decoding the visual stimulus and more time on lexical processing. Shifts in strategy after practice are likely to result in decreases in some brain areas and increases in others, a characteristic pattern of functional reorganization.

This review focuses on studies employing the practice of higher cognitive tasks, where decreases in activity are most often observed. A meta-analysis by Chein and Schneider (2005) identified a set of regions that exhibited decreases in activity after practice across several studies, despite variations in task paradigms and amount of practice. This circuitry, which they suggest may be a domain-general control system, includes prefrontal, medial frontal, posterior parietal, and occipito-temporal cortices. The reduction in activity within this network may reflect a disengagement of control resources and reduced working memory load following sufficient practice (Chein & Schneider, 2005). Similarly, Petersen et al. (1998) describe a “scaffolding” network of regions, including prefrontal cortex and anterior cingulate cortex, which are active during unskilled performance, when the task is novel. Once the task has been practiced and becomes more automatic, however, there is a reduced need for these “scaffolding” resources, and activity in these areas declines.

Poldrack et al. (2005) investigated the neural correlates of automaticity using a dual-task paradigm. Automaticity was defined as the point at which the addition of a second task no longer affected performance on the first task. The task of interest was a sequential reaction time (SRT) task, and the second task was a tone-counting task. Participants performed the single task and dual task while fMRI data were recorded. They then had 3 hour long practice sessions during which they performed both the single and dual tasks, and finally, they were rescanned using the same procedure. Reaction time on the SRT task was measured at each session. Prior to training, reaction time on the SRT task in the dual task condition was significantly longer than the reaction time on the SRT when it was performed alone. After training, however, there was no longer a difference, indicating automaticity. Decreases in brain activity were observed in DLPFC, inferior frontal cortex and caudate nucleus.

The decreased need for control and subsequent disengagement of control regions as a result of automaticity is one mechanism that may explain decreases in functional brain activity that have been observed after practice. As stated above, these decreases are generally seen in the same regions, regardless of task. Increased efficiency in the distributed network underlying a specific task could also result in decreases in functional brain activity (Rypma et al., 2007).

Direct connections between task-related regions may facilitate performance and could result in decreased activity in regions specific to the practiced task. Increased efficiency after practice may result in a “cleaner” map of the activity supporting the task of interest, as processes supporting learning and responding to novelty, as well as those associated with discarded strategies should no longer be evident after practice (Garavan et al., 2000).

A study by Haier et al. in 1992, was one of the first studies to investigate changes in brain function after practice of a cognitive task. They used PET to measure glucose metabolism on two occasions, 4-8 weeks apart, while participants played a visuospatial motor video game. Performance on the task improved significantly after practice, and the participants exhibited decreases in glucose metabolism, suggesting that extraneous processes were pruned resulting in a more efficient circuitry.

This pattern of activity decreases in regions associated with task performance has been observed numerous times using fMRI since Haier et al. (1992) first did their study. Often studies find decreases in both the domain general network and the task specific network. For example, following practice of a visuospatial working memory task, Garavan et al. (2000) observed decreases in activity in regions of frontal, parietal, cingulate, insular, and occipital cortex, some of which were specific to the visuospatial task and others which were part of the domain-general network. Interestingly, they saw the majority of the decline following moderate practice of the task. Continued practice resulted in few additional changes in brain activity. Kassubek et al. (2001) trained participants over two days to read mirror reversed words. After practice to a criterion level, participants showed a decrease in activation in posterior parietal cortex, premotor regions, and extra-striate cortex, all of which were initially related to the task.

Practice effects on brain activity have also been observed over the course of a single scan session (e.g. Fletcher et al., 1999; Weissman et al., 2002). Participants in a study by Weissman et al. (2002) performed a global/local attention orienting task over the course of 10 fMRI runs. Decreased activity across time was observed in parietal regions, which are associated with orienting attention specific to this task (Weissman et al., 2002), and frontal regions, which are involved in response selection.

While changes in brain activity may occur quickly, such as within one session in the study by Weissman et al. (2002), there is a benefit to measuring brain activity on multiple occasions. Hempel et al. (2004) observed both an increase and a decrease in cortical activity, resulting in an inverted U-shaped curve. After two weeks of training on a visual spatial working memory task, participants showed increased cortical activation in the right intraparietal sulcus/superior parietal lobe and right prefrontal cortex; however, after four weeks of training, activity in these areas showed a decrease. Both parietal and prefrontal regions showed an increase in activation with initial performance improvement and a decrease in activation consistent with the consolidation of performance gains.

Although performance improvements after practice occur in the majority of studies, it is possible to observe changes in functional brain activity without corresponding changes in behavioral performance. Landau et al. (2004) used event-related fMRI to investigate changes in activity during different phases of a working memory task. Nearly all the regions associated with object encoding showed decreased activity after practice, even though participants showed no measurable behavioral improvement. Jaeggi et al. (2003) also found that behavioral measures were not always linearly related to activity in regions supporting those behaviors, suggesting that small changes in brain activity could be occurring before changes in behavior can be observed and measured.

Saccade Practice

Studies investigating the effect of practice specifically on behavior and brain activity during saccade tasks are limited. In a study by Fischer and Ramsperger (1986), participants performed a prosaccade task daily over a two-week period. Reaction times decreased and the percent of express saccades (very fast reaction time saccades) generated increased with practice, an effect that had previously been observed in monkeys (Fischer et al., 1984).

Practice can also decrease reaction time on the antisaccade task, as well as decrease the error rate (Dyckman & McDowell, 2005; Fischer & Hartnegg, 2000). Fischer and Hartnegg (2000) found that actively practicing antisaccade responses was associated with a significant decrease in proportion of antisaccade errors in children with dyslexia. Children who received antisaccade training made 24 percent fewer errors after training, while the children who received prosaccade training improved their antisaccade error rate by less than 5 percent, indicating that post-training results were dependent upon the specific task practiced.

In a study using normal young adults, Dyckman and McDowell (2005) also found that participants trained on the antisaccade task made fewer antisaccade errors (6.3%) at testing after one week. Contrary to the results of Fischer and Hartnegg (2000), however, the participants who were trained on the prosaccade task actually made more antisaccade errors (9.3%) the second time they were tested. This pattern of results was expected given that training on the prosaccade task is essentially the same as practicing to make an error on the antisaccade task. Participants trained on a fixation task showed no change in percentage of antisaccade errors after practice. In both studies, participants in all practice groups had faster latencies to correct antisaccades, but only participants who practiced the prosaccade task exhibited faster prosaccade latencies.

How practice affects the circuitry specific to saccade tasks has not been extensively studied. In fact, only one previous study has examined changes in brain activity following saccade practice (Dyckman et al., in preparation). FMRI data were collected while participants performed pro- and anti-saccades in the scanner at two different points; 1) before and, 2) after one week of practice. Each group practiced only one type of eye movement (antisaccades, prosaccades, or fixation) on a hand-held device designed for this purpose (Fischer et al., 2000a).

While many saccade-related regions showed stable activation from the first to the second test session, there were specific areas that demonstrated changes across time. Activity in right DLPFC decreased from the first to the second fMRI session. This decrease was common to all three practice groups, which is consistent with the role of right DLPFC in working memory and response selection (see Bunge, 2004; Curtis & D'Esposito, 2003a for reviews). By the second test session, the task was no longer novel to the participants, and they may have required less working memory to remember the task instructions. This result does not necessarily mean that DLPFC is not involved in antisaccade performance; it simply suggests that DLPFC has a more general role in cognitive control that extends beyond saccade tasks. Right DLPFC signal was still evident during the second test session, but it was weaker than at the first.

Supplementary eye field activity also decreased across time across practice groups. This decrease may reflect an increase in efficiency due to the fact that the participants had performed the antisaccade task before. A decrease in activation in the same anatomical structures supporting the initial performance of the skill is the most common finding within the practice literature (see Kelly & Garavan, 2005 for a review), and researchers have suggested that practice increases the efficiency of the neural circuitry necessary to perform the practiced task (e.g. Jansma et al., 2001; Kassubek et al., 2001; Tomasi et al., 2004).

There were also two areas that showed changes in brain activity only for specific practice groups, which is also consistent with the theory of increased efficiency after practice. Lateral FEF, which are involved in saccade triggering, showed decreases in activity only in the groups that practiced saccade tasks. The antisaccade group and the prosaccade group showed reduced activity in lateral FEF after practice, but the fixation group showed no changes across time. In precuneus, activity decreases after practice were only evident in the group that practiced the antisaccade task. Precuneus, which is in posterior parietal cortex, may be involved in the sensorimotor transformation required to generate an antisaccade to the correct location (e.g. Medendorp et al., 2005; Zhang & Barash, 2000). The antisaccade practice group was the only group to practice this spatial transformation, and thus, only these participants exhibited increased neural efficiency in precuneus while performing antisaccades.

Based on previous studies employing the same practice methods (Dyckman & McDowell, 2005; Fischer & Hartnegg, 2000), it was expected that practicing the antisaccade task would result in improved antisaccade performance at the second test session; however, performance remained the same. One possible explanation as to why practice did not affect antisaccade performance in this study is that the practice sessions may not have been similar enough to the actual test sessions, and therefore no transfer of training took place. The test sessions in this study involved switching between two tasks within one run, as well as alternating between three different tasks during one test session. In contrast, each participant practiced only one task, which was presented in one block of 200 trials per day. The test sessions in the Dyckman and McDowell (2005) study, which found significant changes in performance based on practice group, did not require task switching, making them more similar to the practice sessions.

Summary

Previous research on the behavioral characteristics of saccades and the neural circuitry supporting saccadic eye movements has resulted in a wealth of information about the saccadic eye movement system, which is the foundation for investigating how saccade behavior and neural circuitry may be changed with practice. The practice literature also informs the hypotheses of the present study, specifically how practicing a cognitive task results in changes in functional brain activity in regions supporting both cognitive control and specific task performance.

In the present study, behavior and brain activity were measured on six occasions over the course of a week. Participants were tested on both pro- and anti-saccades at the beginning and end of the week while fMRI data were collected, and they practiced one of the saccade tasks between test sessions while EEG data were recorded. The following hypotheses were tested:

Hypotheses

In the behavioral data, practice was expected to affect percent correct and reaction time on the antisaccade task, and the direction of behavioral change should be dependent upon the type of practice in which the participant engages, similar to Dyckman and McDowell (2005). The antisaccade practice group was expected to make fewer errors as well as correct antisaccades with shorter latencies following practice. The prosaccade group was expected to make more antisaccade errors following practice because practicing prosaccades is akin to practicing to make an error on the antisaccade task. The prosaccade group was also expected to make faster prosaccades and an increased proportion of express saccades after practice.

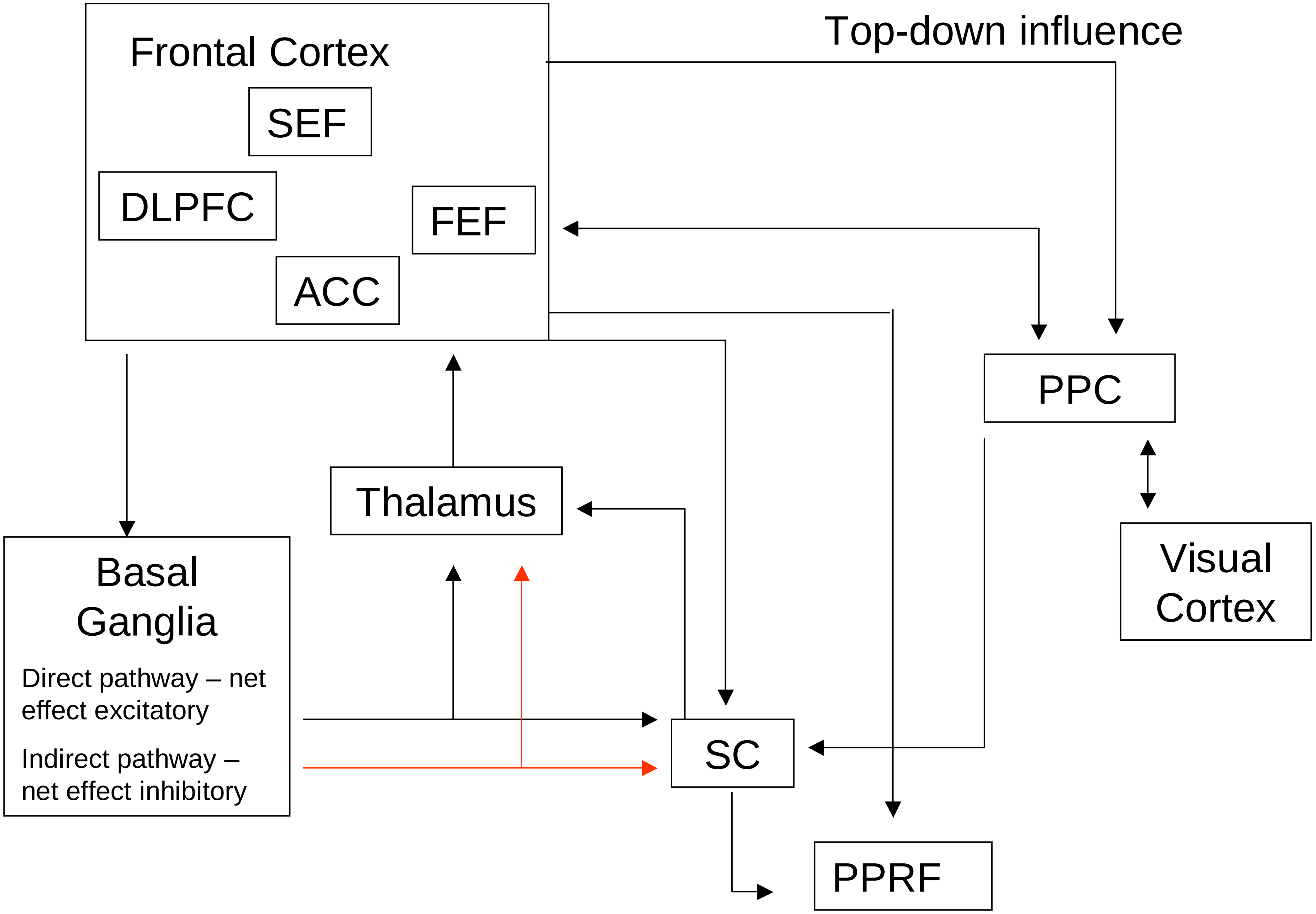
In the imaging data, the spatial extent and the intensity of activity in saccade-related brain regions, as measured by both fMRI and EEG, was expected to change as a result of practice, and the direction of change should be dependent upon the type of task practiced (e.g. antisaccade or prosaccade). Given the extant data on practice-related changes in behavior and brain activity, antisaccade practice was predicted to make performance less effortful. This may result in changes in both the intensity and extent of activation in antisaccade-related brain regions, specifically DLPFC. As participants practiced antisaccades and improved performance, DLPFC activity was expected to decrease because the task became more automatic and required less cognitive control (e.g. Jansma et al., 2001; Tomasi et al., 2004). In contrast, practice of the prosaccade task should make performance of the antisaccade task more effortful, and an increase in DLPFC may be observed in the prosaccade practice group. Given the role of DLPFC in working memory, however, it was possible that the prosaccade group would also show a decrease in antisaccade-related DLPFC activity after practice due to the fact that the tasks are no longer novel (Dyckman et al., in preparation). No changes in DLPFC activity during the prosaccade task were expected as the prosaccade task requires little to no cognitive control. Thus, the domain-general system for cognitive control should not be evident during the prosaccade task during any of the test or practice sessions.

In addition to changes in DLPFC, it was expected that specific saccade-related regions would show decreases after practice, similar to Dyckman et al. (in preparation). As both groups were practicing saccades, lateral FEF should show a decrease in saccade-related activity across time. Finally, changes in precuneus should be observed for the antisaccade practice group only because the antisaccade group practiced the coordinate transformation necessary for the antisaccade task. The practice stimuli for the proposed experiment were exactly the same as the test stimuli, including eccentricity of the peripheral cues. This is an improvement over the previous study (Dyckman et al., in preparation), and should make it more likely that the neural circuitry supporting the coordinate transformation will function more efficiently, and therefore show a decrease in activity over time.

With the EEG data, it is possible to eliminate incorrect trials, examine activity that occurs prior to stimulus presentation (gap period), and separate trials to left and right stimuli. The introduction of a temporal gap between fixation offset and stimulus onset results in faster latencies for both pro- and anti-saccades. As such, the examination of brain activity during this period may provide important information regarding the mechanism of express saccades. It was expected that activity during this preparatory period would be greater after practice, when participants were generating more express saccades.

The separation of trials based on stimulus location allowed for the investigation of occipital and parietal activity contralateral to where the stimulus was presented. In the McDowell et al. (2005) EEG/MEG study, the strength of activity in visual cortex contralateral to the stimulus was decreased for antisaccades compared to prosaccades, which may reflect less investment in the stimulus location during antisaccades, since participants are not supposed to look at the stimulus. After antisaccade practice, activity in contralateral visual cortex may exhibit even less activation prior to antisaccade generation, which would facilitate correct performance (less likely to glance toward the stimulus). If this is the case, it may help to explain why participants make fewer antisaccade errors after practicing the antisaccade task.

<u>Figure 2.1</u> Neural Circuitry of Saccades
Circuitry connecting brain regions involved in saccade generation. Black lines indicate excitatory connections. In the case of the connections between the basal ganglia and the superior colliculus and thalamus, the black line indicates that the net effect of the direct pathway is excitatory and the red line indicates that the net effect of the indirect pathway is inhibitory.



Frontal Cortex

SEF

DLPFC

FEF

ACC

Top-down influence

PPC

Visual Cortex

Thalamus

Basal Ganglia

Direct pathway – net effect excitatory

Indirect pathway – net effect inhibitory

SC

PPRF

CHAPTER 3

METHODS

Participants

Participants (N=32) were recruited through the undergraduate psychology research pool (M age = 19.2, SD = 1.1; 100% female). Subjects were in good physical health, absent of known neurological hard signs, and provided informed consent. This project was approved by the University of Georgia Institutional Review Board (UGA IRB #10387). Exclusion criteria included brain injury, neurological disease, or a history of severe head trauma. History of drug or alcohol abuse was also means for exclusion. Additionally, participants were screened for contraindications for fMR imaging (i.e. eliminated for 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, plates, wires).

Procedure

FMRI data were acquired on two occasions while participants engaged in saccade tasks (Table 3.1: “Study Schedule” below). Between fMRI sessions, participants practiced an assigned eye movement task each day while EEG data were recorded. Sixteen participants practiced the antisaccade task, and 16 participants practiced the prosaccade task.

FMRI Sessions

FMR imaging was conducted at Athens Orthopedic Clinic MRI Center on a 1.5T GE Signa Horizon LX MR system. Prior to scanning, participants were given instructions and shown illustrations of the three tasks. Once in the scanner room, participants lay in a supine position on the gurney, and their head positions were stabilized with foam padding and a velcro strap placed across the forehead to restrict head movement. A mirror was placed over the participant's head to allow her to see a screen placed near her feet.

Eye movements were recorded using an fMRI compatible eye tracking system (Meyetrack, SensoMotoric Instruments, Inc.). A second mirror placed over the participant's head projected the image of the participant's eye to an infrared camera placed at the back of the magnet bore. Prior to the first task, subjects fixated on calibration targets at central fixation and at the four corners of the visual display. Eye movement recordings were digitized at 60 Hz, displayed on a computer monitor so performance could be monitored continuously by the experimenter, and recorded for later analysis. This system was used successfully to collect eye movement data for two previous projects (Camchong et al., 2006; Dyckman et al., 2007).

Two localizer images were taken at the beginning of the session to ensure optimal brain coverage for each participant. A high-resolution structural image was obtained (SPGR – protocol: sagittal, 2NEX, .9375 x .9375 x 1.5 mm, 124 slices, TE=2.8ms, TR=10.8ms, flip angle=20 degrees, scan time=5 min 41 sec). Following the structural image, 3 functional runs were collected (spiral scan w/ 2 interleaves, 24 continuous axial slices, 3.75 x 3.75 x 4 mm, TE=40ms, TR=1912ms, flip angle=77 degrees, scan time = 5 min 1 sec).

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 et al., 2006; Dyckman et al., 2007; McDowell et al., 2002). Each run consisted of 13 alternating blocks of a baseline and an experimental condition (see Figure 3.1). The fixation/prosaccade run alternated between blocks of fixation and blocks of 8 prosaccade trials. The fixation/antisaccade run alternated between blocks of fixation and blocks of 8 antisaccade trials. The prosaccade/antisaccade run alternated between blocks of 8 prosaccade trials and blocks of 8 antisaccade trials. The order of the runs was counterbalanced across participants; however, the prosaccade/antisaccade run always appeared last.

Practice/EEG Sessions

Participants completed 3 practice runs per day over one week. The prosaccade practice group completed three runs of alternating blocks of fixation and prosaccades, identical to the fixation/prosaccade run described above. The antisaccade practice group completed three runs of alternating blocks of fixation and antisaccades, identical to the fixation/antisaccade run described above. Participants received a short break after each run. All participants completed 144 saccade trials per day.

EEG data were recorded vertex-referenced using a 256 channel Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI, Eugene, OR) at the UGA facility. Electrode impedances were kept below 50 kΩ, which is standard when using high input impedance amplifiers like those from EGI. Data were sampled at 500 Hz with an analog filter bandpass of 0.1–200 Hz. Eye movements were recorded using horizontal EOG placed at the outer canthi of the eyes.

Stimuli

Visual stimuli consisted of three different tasks. 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. Healthy participants make a larger number of errors on antisaccade tasks when a gap exists (e.g. Fischer et al., 2000b; McDowell & Clementz, 1997).

Fixation (see Figure 3.1)

A small white cross was presented at central fixation for 22.4 seconds. The participant was instructed to fixate on the cross as it remained in the center of the screen.

Prosaccade (see Figure 3.1)

A fixation cross with a square around it was presented at central fixation to start the trial and remained there for 1600 ms. The center stimulus was extinguished, and 200ms later (gap), a 2.5 deg grey dot was presented ± 8 degrees from fixation in the horizontal plane for 1000 ms (half in each visual field). Participants were instructed to move their eyes to the dot as quickly and accurately as possible.

Antisaccade (see Figure 3.1)

The stimuli and timing for the antisaccade task were identical to those for the prosaccade task except that the fixation cross was surrounded by a diamond 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.

Analysis

Eye Movement Data

Eye movement data obtained while participants were in the MR scanner were scored using programs written in MATLAB (The Mathworks Inc., Natick, MA). Eye movement data obtained during practice sessions in the EEG environment were scored using BESA. Trials with blinks in the presaccade period (from 350ms 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.

A separate reaction time histogram was created for pro- and anti-saccades to determine the outlier values for each task type (see Figure 3.2). The pro-saccade histogram was also used to confirm the existence of an express saccade peak.

The number of correct trials in each run was divided by the total number of useable trials for each condition and multiplied by 100 to compute percentage correct. For the eye movement data collected during the fMRI test sessions, separate 2x2x2 repeated measures ANOVAs (Between Subjects factor: group; Within Subjects factors; session, run type (e.g. prosaccades during: fixation/pro run, pro/anti run) were used to examine the effect of group, practice, and context on prosaccade latency, proportion of express prosaccades, antisaccade latency, the percentage of correct antisaccades, and saccade gain.

For the eye movement data collected during the EEG practice sessions, a 2x4 repeated measures ANOVA (BS factor: task; WS factor; session) was used to examine the effect of task and practice on latency. For the prosaccade practice group, a one-way ANOVA was used to examine the effect of practice on the proportion of express saccades generated. For the antisaccade practice group, a one-way ANOVA was used to examine the effect of practice on the percentage of correct antisaccades. Planned comparisons were used to determine whether the percent correct at the first EEG session was significantly different from percent correct at any of the subsequent sessions, which would indicate performance improvement.

FMRI Data

Analyses were conducted using Analysis of Functional Neuroimages (AFNI; Cox, 1996), similar to Camchong et al., 2006 and Dyckman et al., 2007. Three dimensional datasets were created from individual image files. Images from the second fMRI session were aligned with the images from the first fMRI session for more accurate comparisons across scanning sessions. For each run, volumes were registered to a middle volume to correct for minor head movement, and a 4mm full width half maximum (FWHM) Gaussian filter was applied to the data to account for individual variations in anatomy. For each voxel, the percent change in BOLD signal from baseline was calculated for each of the 75 time points (the first two and last volumes were eliminated).

A hybrid independent component analysis (ICA) was then performed, similar to the approach described by McKeown (2000) and identical to the procedure used by Dyckman et al. (2007). 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 dataset was transformed into standardized space (based on the Talairach and Tournoux Atlas, 1988), and an average dataset for each run 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). The six averages (one for each run each day) were concatenated in space, and Probabilistic ICA (PICA) was performed using MELODIC (Beckmann & Smith, 2004). PICA yielded 27 spatially independent components, the first two of which had time courses with the same peak frequency as the experimental design (see Figure 3.3).

For each subject, for each run, the percent signal change across time was correlated with the first two PICA components, while 14 of the remaining components were used as artifact and/or motion regressors, to detect areas that were associated with the experimental task in each run. The artifact components were chosen based on visual inspection of the spatial distribution and the peak frequency of the components. For example, later components with the same peak frequency as earlier components were not included as artifact regressors.

Data collected on the first day of scanning were collapsed across groups for an initial analysis, as these data were collected prior to the assignment of practice groups. For each run, a one-sample t-test versus 0 (N=32) was conducted to determine which areas of the brain showed increased BOLD signal related to the experimental task. To protect against false positives, a threshold/cluster method derived from Monte-Carlo simulations (accounting for the 4 mm FWHM Gaussian filter and with a connectivity radius of 5.6 mm) was applied to *t* maps (Ward, 1997). Based on these simulations, the familywise alpha of .05 was preserved with an *a priori* voxelwise probability of .015 and three-dimensional clusters with a minimum volume of 704 μL (11 or more voxels).

The nature of the relationship between test sessions in the brain regions with significant saccade-related activity was examined via a region of interest (ROI) analysis. The clustered *t* map from the fixation/anti run (collapsed across both fMRI sessions) was used to identify regions of interest (ROI) because, of the three runs, the fixation/anti run shows the largest percent signal change in the saccade circuitry (Dyckman et al., 2007), and thus provides the most inclusive set of regions for ROI analyses.

A spherical ROI (radius 8 mm) was positioned at the center of mass of each region that showed significant antisaccade-related activity during the fixation/anti run. Mean percent signal changes for each run were calculated for each ROI for each individual, and submitted to a 2 x 2 ANOVA with practice group as the between-subjects factor and test session as the within-subjects factor.

EEG Data

Data Screening

EEG data were pre-processed as in published studies (e.g. Gilmore et al., 2005a, 2005b). Bad sensors were interpolated (no more than 5% of sensors for any subject on any day) using a spherical spline interpolation method as implemented in BESA 5.1 (MEGIS Software, Grafeling, Germany). The data were segmented around stimulus triggers to create stimulus-locked averages. Data were inspected for blink and cardiac artifacts within the epochs of interest (see below). If present (blink artifact – 3 datasets out of 128 total, ekg artifact – 3 datasets out of 128 total), artifacts were corrected using a spatial filtering algorithm in BESA (Berg & Scherg, 1994; Ille, Berg, & Scherg, 2002). The data were transformed to an average reference and digitally filtered using a 1 Hz lowpass filter, a 40 Hz highpass filter, both in the forward direction only, and a 60 Hz notch filter. Trials with activity greater than 120uV were automatically eliminated from trial averaging. Remaining trials were baseline-adjusted using the first 150ms of the defined epoch and averaged.

Averages

Individual stimulus-locked averages were created for each stimulus location (left or right) for each day (1-4) for the following conditions:

Prosaccades

Stimulus-locked epochs began 350ms prior to stimulus onset (150ms prior to gap) and ended 250ms after stimulus presentation.

All – Correct saccades with latencies between 90ms and 240ms.

Regular- Correct saccades with latencies between 145ms and 240ms.

Express – Correct saccades with latencies between 90ms and 135ms.

Antisaccades

Stimulus-locked epochs began 350ms prior to stimulus onset (150ms prior to gap) and ended 400ms after stimulus presentation.

Regular- Correct antisaccades with latencies between 110ms and 400ms.

Analyses of ERP Voltage Data

Component latency identification and statistical analyses of voltage data were performed using programs written in Matlab (version 7.0, MathWorks, Natick, MA).

Gap Period Activity

Because gap period activity ocurred prior to stimulus onset (200ms prior to stimulus onset until stimulus onset), trials to left and right stimulus locations were averaged. To identify components above baseline noise level during this period, a global field power (GFP) plot was derived from the grand averaged data from all participants on all days. There were identifiable peaks for both pro- and anti-saccades at -92ms and -14ms (see Figure 3.4a). Negative values on the x-axis indicate time points prior to the onset of the peripheral stimulus.

Statistical comparisons of scalp potential amplitudes were conducted for the components of interest. Scalp potentials were averaged across 10ms time windows for each component of interest. This resulted in a mean value for each component for each subject for each sensor for each day. For each component, a repeated measures ANOVA with factors Task (AS, PS) and Day (1,2,3,4) was conducted separately for each sensor. To account for multiple comparisons, a cluster threshold technique similar to that used for the fMRI data was used. The rules were for statistical significance were derived through Monte Carlo simulations as implemented in AFNI (Cox, 1996). To maintain a familywise alpha level lower than .05, the following conditions had to be met: 1) an individual test at a given sensor was significant at p<.035, and 2) at least 5 neighboring sensors were also significant at p<.035.

Simple effects were then evaluated in areas showing significant differences. For clusters where there was a significant effect of task, scalp potentials within the cluster were averaged and collapsed across days, resulting in separate prosaccade and antisaccade means, which were then subjected to t-tests. For clusters in which there was a significant effect of day, scalp potentials within the cluster were averaged and collapsed across tasks, and a one-way repeated measures ANOVA was performed. Finally, for clusters in which there was a signficant interaction, scalp potentials were averaged across the cluster, separately for each day within each task condition (e.g. prosaccade day 1, antisaccade day 1, etc.). Simple main effects were evaluated with one-way repeated measures ANOVA, separately for antisaccades and prosaccades. If the one-way ANOVA was significant for one or both of the tasks, a trend analysis was performed to test for a linear trend across EEG sessions.

Antisaccade Stimulus Registration and Vector Inversion

Two components above baseline noise level were identified in the antisaccade data around 102ms and 130ms after stimulus onset (see Figure 3.4b). The peak amplitude in each individual plot that was closest in time to the grand averaged peak for each component was identified. Thus, each antisaccade subject on each day had one value for the earlier peak and one for the later peak. Time windows were not used because the two components were close together in time and averaging across timepoints would have resulted in overlapping activation.

Statistical comparisons of scalp potential amplitudes were conducted for each of the components of interest. For each component, a repeated measures ANOVA with factors Stimulus

Location (Left, Right) and Day (1,2,3,4) was conducted separately for each sensor. Cluster thresholding was applied as described above.

Simple effects were evaluated in areas showing significant differences. For clusters where there was a significant effect of stimulus location, scalp potentials within the cluster were averaged and collapsed across days, resulting in separate left and right means, which were then subjected to t-tests. For clusters in which there was a significant effect of day, scalp potentials within the cluster were averaged and collapsed across stimulus locations, and a one-way repeated measures ANOVA was performed. Finally, for clusters in which there was a signficant interaction, scalp potentials were averaged across the cluster, separately for each day within each task condition (e.g. left stimulus day 1, right stimulus day 1, etc.). Simple main effects were evaluated with one-way repeated measures ANOVA, separately for left and right stimuli. If the one-way ANOVA was significant for one or both of the stimulus locations, a trend analysis was performed to test for a linear trend across EEG sessions.

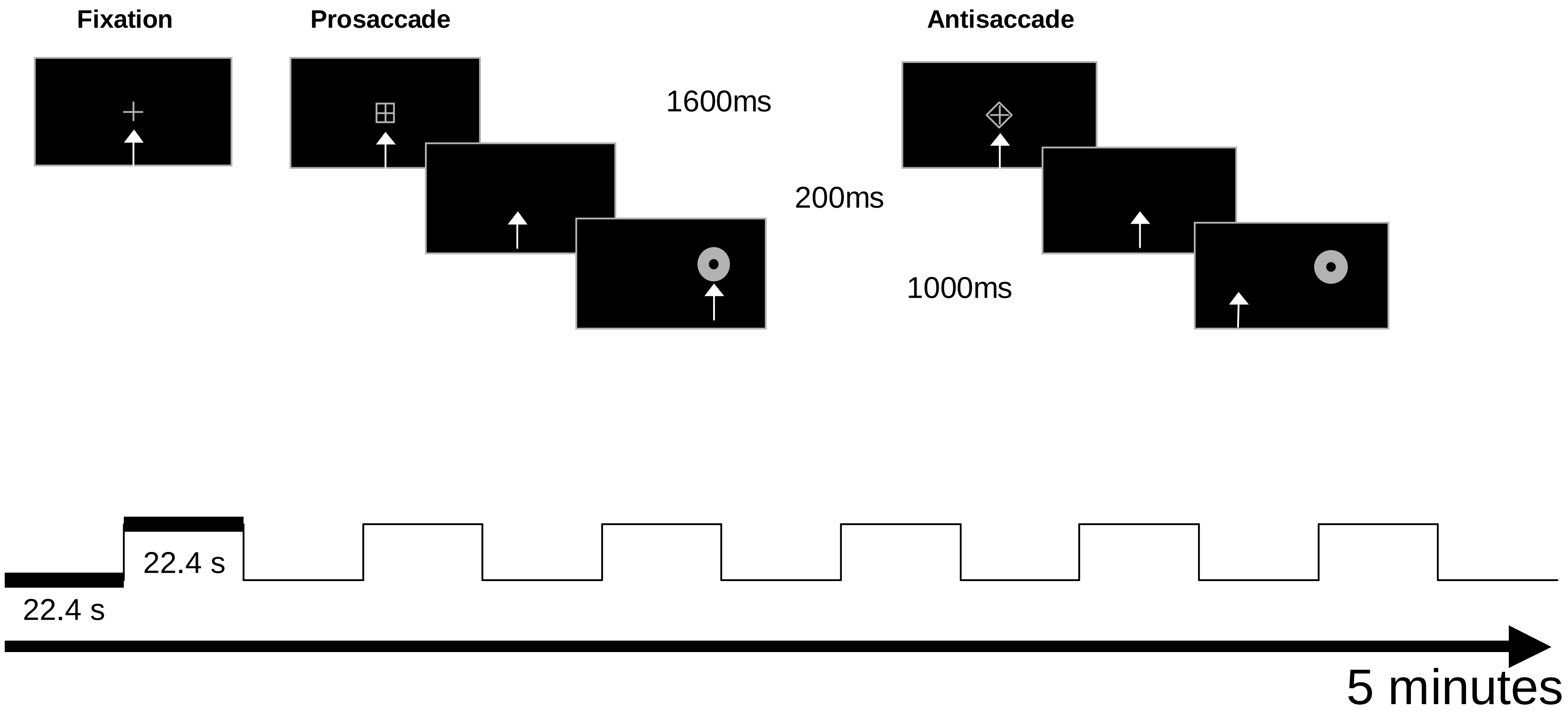
Distributed Source Analysis

Distributed source analysis was used to estimate the source activity associated with significant voltage differences. For each significant difference, voltages from one condition were subtracted from the other condition (e.g. antisaccade with right stimulus subtracted from antisaccade with left stimulus), resulting in a voltage plot of the difference. This source of this difference was then modeled using L2 minimum norm estimation (Hamalainen & Ilmoniemi, 1984). In this approach, fixed source locations on the cortex are specified a priori and source strength values are estimated for each location at each time point based on the data recorded at the sensor locations. Minimum norm estimation was done using BESA 5.1, which estimates activity at 713 locations evenly distributed across the surface of a smoothed standard MRI of the cortex.

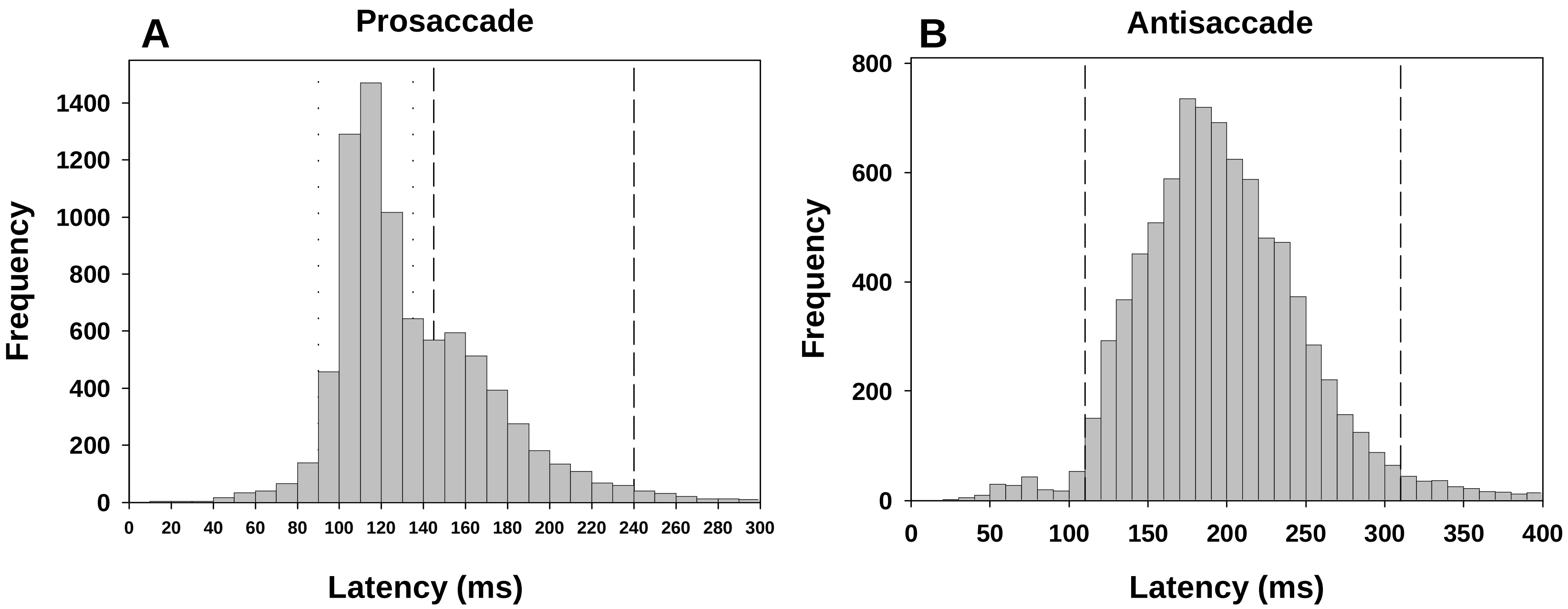
Table 3.1

Study Schedule.

	Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
Week 1						FMRI #1 (F1)	
Week 2		EEG #1 (E1)	EEG #2 (E2)	EEG #3 (E3)	EEG #4 (E4)	FMRI #2 (F2)	



<u>Figure 3.1</u> Stimuli and Block Design
Stimuli used for (A) fixation, (B) prosaccades, and (C) antisaccades. The arrow indicates where the participant should be looking at each point in time. The fixation/prosaccade run consisted of alternating blocks of fixation and 8 prosaccade trials. The fixation/antisaccade run consisted of alternating blocks of fixation and 8 antisaccade trials. The prosaccade/antisaccade run consisted of alternating blocks of 8 prosaccades and 8 antisaccades.



<u>Figure 3.2</u> Latency Histograms
Distribution of a) prosaccade and b) antisaccade latencies across EEG sessions. In the left plot, the latencies between the dotted lines represent express prosaccades (90-135ms) and the latencies between the dashed lines represent regular prosaccades (145-240ms). In the right plot, the latencies between the dashed lines represent antisaccades that were included in analyses (110-310ms).

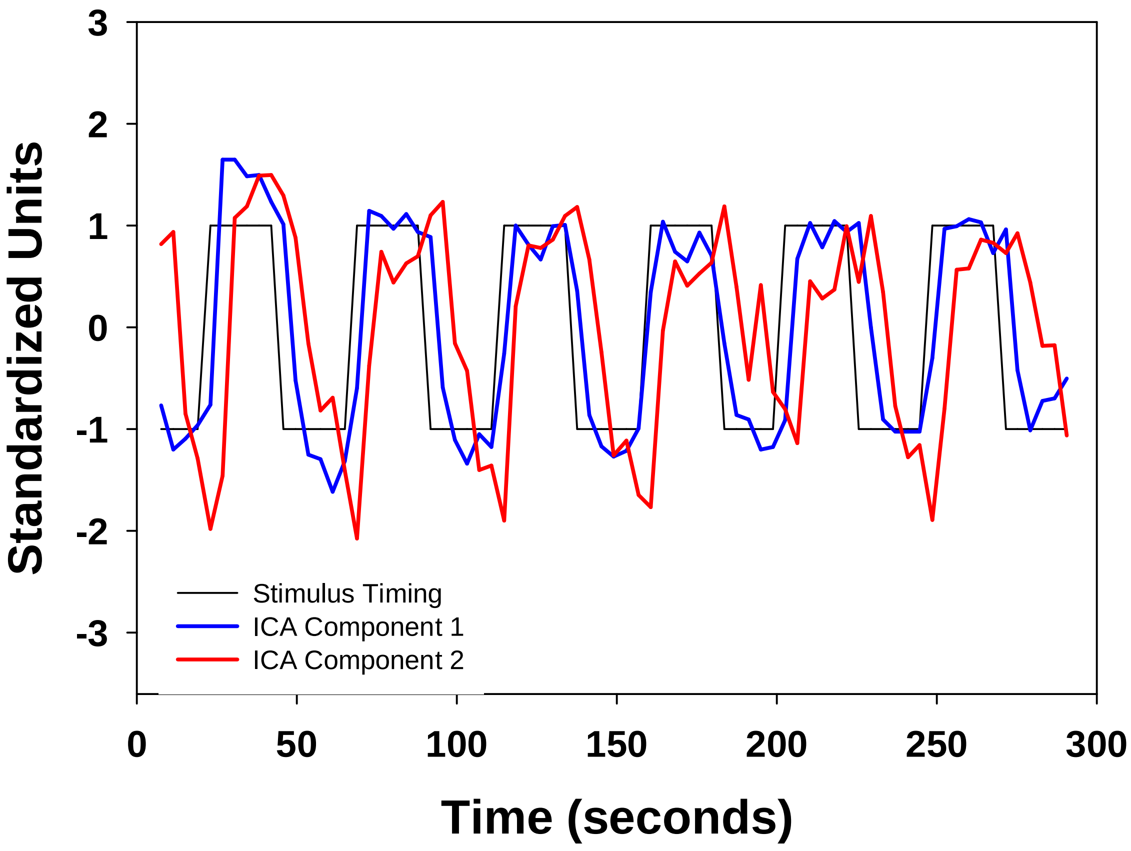
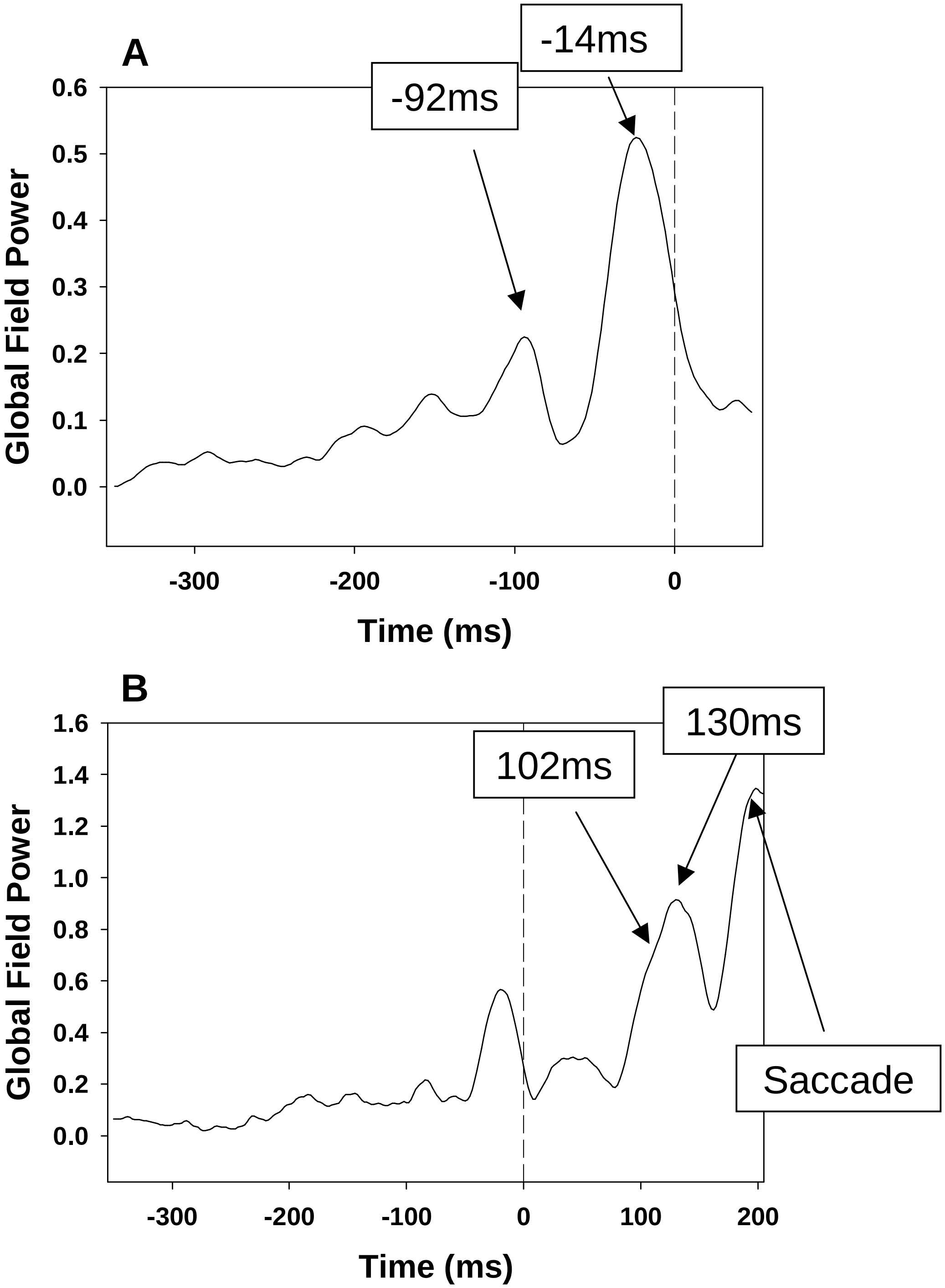


Figure 3.3 **Stimulus Timing and ICA Components**
Plots of stimulus presentation (black line) and task-related ICA components across the length of a run. For the stimulus presentation plot, -1 represents the baseline condition, +1 represents the experimental condition. Component 1 is shown in blue, component 2 is shown in red. Note that although there is much overlap between the components, component 2 is shifted 1 TR (3.824secs) to the right.



<u>Figure 3.4</u> Global Field Power Plots
Plots of global field power (GFP) for a) grand average of prosaccades and antisaccades across EEG sessions prior to stimulus presentation and b) grand average of left and right antisaccades across EEG sessions prior to saccade generation. Timepoints that showed above baseline activity in the GFP plots were examined for effects of session and either task or stimulus location.

CHAPTER 4

RESULTS

Eye Movement Data

FMRI Sessions

A complete set of eye movement recordings was obtained for 30 of the 32 participants. In both cases, failure to record a participant's eye movement data was due to technical difficulties associated with the position of the eye relative to the infrared light source or an insufficient contrast between the pupil and the iris.

Percent Correct

For the percentage of correct prosaccades, there was a main effect of run type ($F_{1,28}$ = 8.203, p = .008; see Figure 4.1). Participants generated an increased percentage of errors on the prosaccade task during the mixed saccade run (M = 98.5%, SE = .4) compared to the single saccade run (M = 99.8%, SE = .1). There were no effects of group or session on percentage of correct prosaccades.

For the percentage of correct antisaccades, there were no significant effects of group, session, or run type (M = 85.7%, SE = 1.6; see Figure 4.1).

Latency

For prosaccade latency, there was a significant group by session effect ($F_{1,28}$ = 5.797, p = .023; see Figure 4.2a). The prosaccade practice group showed decreased prosaccade latencies from the first session (M = 181.7ms, SE = 5.6) to the second session (M = 169.1ms, SE = 4.4), while the antisaccade practice group showed no change in prosaccade latency (M = 177.4ms, SE

= 4.1). There was no significant effect of run type (i.e. fixation/prosaccade run, prosaccade/antisaccade run).

For antisaccade latency, there was a main effect of session ($F_{1,28}$ = 36.637, p < .001; see Figure 4.2b). Reaction time decreased from the first session (M = 243.0ms, SE = 4.7) to the second session (M = 220.8ms, SE = 4.4). There was also a significant session by run type interaction ($F_{1,28}$ = 5.648, p = .025; see Figure 4.2d). There was a greater decrease in latency from the first session to the second session for the single saccade run (M1 = 246.2ms, SE1 = 5.0; M2 = 218.1ms, SE2 = 4.6) than for the mixed saccade run (M1 = 239.8ms, SE1 = 4.9; M2 = 223.4ms, SE2 = 4.4).

Proportion of Express Saccades

Express saccades are observed for prosaccades only. For the proportion of express prosaccades, there was a significant group by session effect ($F_{1,28}$ = 6.788, p = .015; see Figure 4.2c). The prosaccade practice group exhibited an increase in the proportion of express saccades generated from the first session (M = 26.7%, SE = 5.0) to the second session (M = 40.4%, SE = 6.1), while the antisaccade practice group showed no change in proportion of express saccades (M = 33.5%, SE = 5.3). There was also a significant effect of run type ($F_{1,28}$ = 10.615, p = .003). Participants generated more express saccades during the mixed saccade run (prosaccade/antisaccade; M = 36.3%, SE = 4.1) compared to the single saccade run (fixation/prosaccade; M = 30.8%, SE = 3.6).

Gain

For prosaccade gain, there was a significant effect of run type ($F_{1,28}$ = 8.18, p = .008; see Figure 4.3). Participants were more accurate during the mixed saccade run (M = 1.02, SE = .025) than during the single saccade run (M = 1.08, SE = .025). There were no effects of group or session on prosaccade gain.

For antisaccade gain, there was a significant effect of run type ($F_{1,28}$ = 35.1, p < .001; see Figure 4.3). Participants slightly overshot the target location during the single saccade run (M = 1.07, SE = .048) and slightly undershot the target location during the mixed saccade run (M = .95, SE = .044). There were no effects of group or session on antisaccade gain.

EEG Practice Sessions

Percent Correct

There were no significant effects of practice session on the percentage of correct prosaccades (M = 99.7%, SE = .1). The overall effect of practice session on the percentage of antisaccades was not significant ($F_{3,45}$ = 2.49, p = .07), however the results of planned comparisons indicate that participants improved their percentage correct from the first session (M = 85.1%, SE = 2.6) to the third session (M = 89.4%, SE = 2.1; t_{15} = 4.4, p = .001; see Figure 4.4). Performance at the fourth and final EEG session did not significantly differ from performance at the third session (t_{15} = 1.22, p = .24).

Latency

For saccade latency, there was a main effect of task ($F_{1,30}$ = 70.25, p < .001). Prosaccade latencies (M = 134.8ms, SE = 4.9) were faster than antisaccade latencies (M = 192.9ms, SE = 4.9). There was also a main effect of practice session ($F_{3,90}$ = 2.90, p = .039; see Figures 4.5a and 4.5b). A trend analysis revealed a significant linear trend ($F_{1,30}$ = 6.74, p = .014). Latencies decreased across practice sessions for both tasks.

Proportion of Express Saccades

The proportion of express saccades over time was analyzed for the prosaccade task. There was a main effect of session ($F_{3,45}$ = 3.561, p = .021; see Figure 4.5a). A trend analysis revealed a significant linear trend ($F_{1,30}$ = 8.16, p = .012). Participants generated an increased percentage of express saccades across sessions.

FMRI Data

Day 1 Results

For each run, areas that exhibited increased BOLD signal during the experimental condition compared to the baseline condition were similar to those seen in previous studies (e.g Dyckman et al., 2007). They included SEF, FEF, regions of posterior parietal cortex, visual cortex, basal ganglia and thalamus, as well as right DLPFC for the antisaccade task. Regions are shown in Figure 4.6 and Table 4.1.

Changes in Brain Activity over Time

Region of interest (ROI) analyses were employed to examine the effect of practice on brain activity. Talaraich coordinates for the ROIs derived from the fixation/antisaccade run are listed in Table 4.1.

Fixation/Prosaccade Run

There were significant main effects of test session in inferior frontal gyrus (IFG; $F_{1,30}$ = 6.43, p = .017) and inferior parietal lobule (IPL; $F_{1,30}$ = 5.63, p = .024). In both of these regions, there was increased BOLD signal contrast at the first session when compared to the second session (see Figure 4.7, Table 4.2). There were no group x session effects on the BOLD signal during the this run.

Fixation/Antisaccade Run

There were significant main effects of test session in right DLPFC ($F_{1,30} = 4.91$, $p = .034$) inferior frontal gyrus (IFG; $F_{1,30} = 10.9$, $p = .002$) and cuneus ($F_{1,30} = 10.7$, $p = .003$). In all of these regions, there was increased BOLD signal contrast at the first session when compared to the second session (see Figure 4.8, Table 4.2).

Three regions showed significant group x test session effects on the BOLD signal during the Fixation/Antisaccade Run: precuneus ($F_{1,30} = 4.28$, $p = .047$), inferior parietal lobule (IPL; $F_{1,30} = 5.66$, $p = .024$), and anterior cingulate cortex (ACC; $F_{1,30} = 4.75$, $p = .037$). For all three regions, a difference score analysis revealed significant differences between groups in the amount of change from the first session to the second (see Figure 4.9, Table 4.2). For precuneus, antisaccade-related activity decreased for the antisaccade practice group (Mdiff = -.074, SE = .048) and increased for the prosaccade group (Mdiff = +.041, SE = .028;). For IPL, antisaccade-related activity decreased for the antisaccade practice group (Mdiff = -.084, SE = .07) and remained constant for the prosaccade practice group (Mdiff = +.002, SE .029). For ACC, antisaccade-related activity decreased for the antisaccade practice group (Mdiff = -.08, SE = .13), and increased slightly for the prosaccade practice group (Mdiff = +.015, SE = .03).

Prosaccade/Antisaccade Run

There was no effect of practice group or session on the BOLD signal during the Prosaccade/Antisaccade run.

EEG Data

Gap Period Activity

For the period prior to stimulus presentation, there were two peaks that were analyzed: 92 ms prior to stimulus onset (-92ms) and 14 ms prior to stimulus onset (-14ms). There was a significant task by session effect at 92ms prior to stimulus onset in right frontal and right occipital sensors. For right frontal sensors, analysis of simple main effects revealed a significant effect of session for antisaccades ($F_{3,45}$ = 2.98, p = .041), but not for prosaccades ($F_{3,45}$ = 1.83, p = .16). Trend analysis on the antisaccade data indicated a significant linear trend ($F_{1,15}$ = 6.29 , p = .024), whereby the responses had smaller amplitudes across sessions; the largest decrease occurring between session 1 and session 2 (see Figure 4.10). Source analysis showed that differences between the first session and subsequent sessions occurred in an area over right occipital cortex and a smaller area over right frontal cortex.

For right occipital/parietal sensors, analysis of simple main effects revealed a significant effect of session for prosaccades ($F_{3,45}$ = 3.07, p = .037, but not for antisaccades ($F_{3,45}$ = 2.26, p = .094). Trend analysis on the prosaccade data indicated a significant linear trend ($F_{1,15}$ = 7.60 , p = .015), whereby the responses had larger amplitudes across sessions; the largest increase occurring between session 1 and session 2 (see Figure 4.11a). Source analysis showed that differences between the first session and subsequent sessions occurred mainly in superior parietal cortex in both hemispheres.

This effect was further investigated by examining the difference between express prosaccades and regular prosaccades at this peak using a paired t-test. This test revealed significant differences between express and regular prosaccades in right occipital sensors; larger amplitude responses were observed for express prosaccades compared to regular prosaccades (see Figure 4.11b). Source analysis on this difference yielded a source in right superior parietal cortex, in a similar location to a source of activity differences between the first session and subsequent sessions described above.

At 14 ms prior to stimulus onset, there were no effects of task or session.

Antisaccade Stimulus Registration and Vector Inversion

For the period after stimulus onset, there were two peaks that were analyzed: 102ms following stimulus onset and 130ms following stimulus onset. There was a significant main effect of stimulus location at 102ms after stimulus onset in left and right occipital sensors. For left occipital sensors, larger amplitude responses were evoked by stimuli presented in the right visual field. For right occipital sensors, larger amplitude responses were evoked by stimuli presented in the left visual field (see Figure 4.12). Source analysis showed that differences between left and right stimuli at 102 ms occurred in left and right visual cortex.

Right occipital sensors also showed a significant stimulus location by session effect at the 102ms peak. Analysis of simple main effects revealed a significant effect of session for stimuli presented in the left hemisphere ($F_{3,45} = 9.78$, $p < .001$), but no effect of session for stimuli presented in the right hemisphere ($F_{3,45} = .99$, $p = .40$). Trend analysis on the left stimuli data indicated a significant linear trend ($F_{1,15} = 65.5$, $p < .001$), whereby the amplitude in response to left visual field stimuli decreased across sessions; pairwise comparisons indicated that sessions 1 and 2 significantly differed from sessions 3 and 4, but did not differ from one another. Likewise, sessions 3 and 4 did not significantly differ from one another (see Figure 4.13). Source analysis showed that, for stimuli presented in the left visual field, differences between the first two sessions and the last two sessions occurred in right visual cortex.

At 130 ms after stimulus onset, there was a significant main effect of stimulus in left and right parietal sensors; the pattern of activity was opposite to that observed at the 102 ms peak. For left hemisphere sensors, larger amplitude responses were evoked by stimuli presented in the left visual field (movement toward right visual field). For right hemisphere sensors, larger amplitude responses were evoked by stimuli presented in the right visual field (movement toward left visual field; see Figure 4.12). Source analysis showed that differences between left and right stimuli at 130 ms occurred in left and right parietal cortex.

Table 4.1

Talairach Coordinates of the Centers of Mass for ROIs.

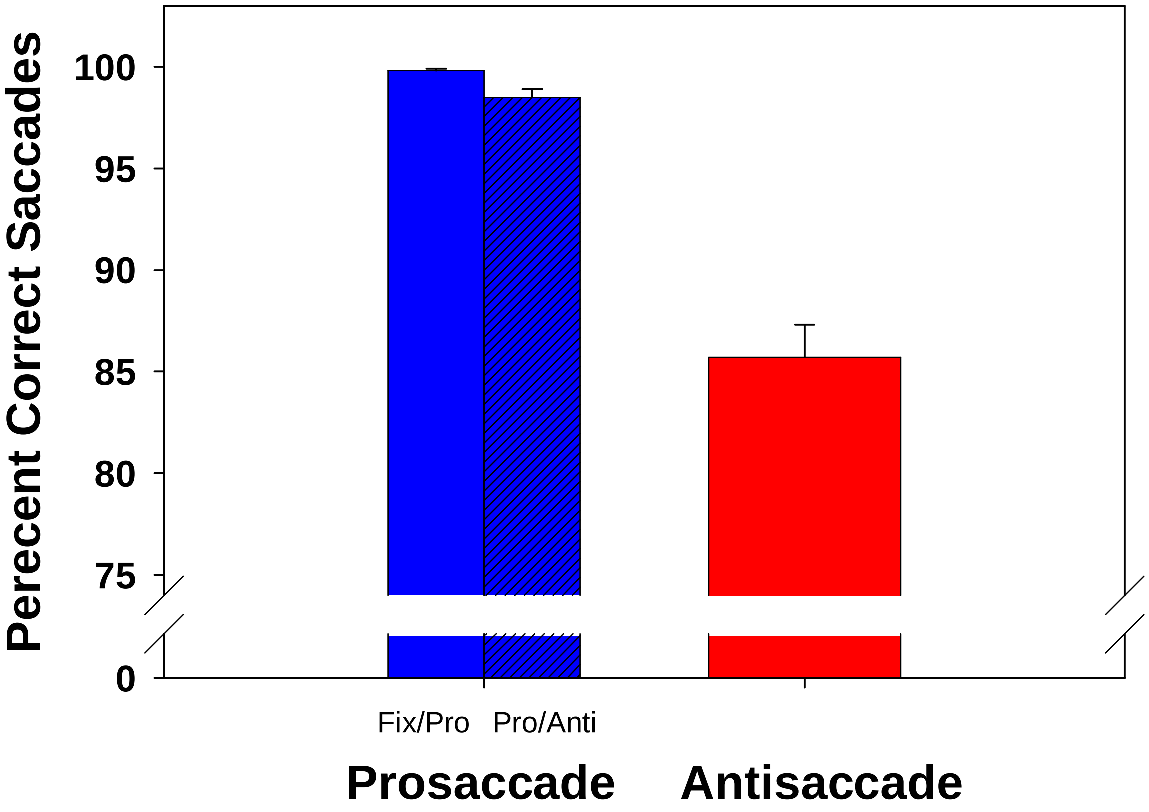
ROI	L/R	X	Y	Z
SEF[a]		-1	-2	+52
Lat FEF[b]	L	-42	-3	+50
	R	+42	-6	+52
Med FEF[c]	L	-27	-3	+56
	R	+24	-9	+57
DLPFC[e]	R	+36	+36	+34
Precuneus[d]	L	-19	-72	+52
	R	+10	-72	+48
IFG[h]	L	-49	+15	+6
	R	+43	+12	+5
IPL[g]	L	-42	-34	+34
	R	+52	-46	+23
ACC[f]	L	-8	+13	+37
	R	+5	+16	+36
Cuneus[k]	L	-11	-73	+6
	R	+5	-72	+6
Middle Occ[l]	L	-31	-86	+21
	R	+25	-85	+18
Striatum[i]	L	-12	0	+17
	R	+10	+1	+17
Thalamus[j]	L	-7	-14	+14
	R	+4	-14	+13

Letters in superscript font next to ROIs correspond to the lowercase letters in Figure 4.6

Table 4.2

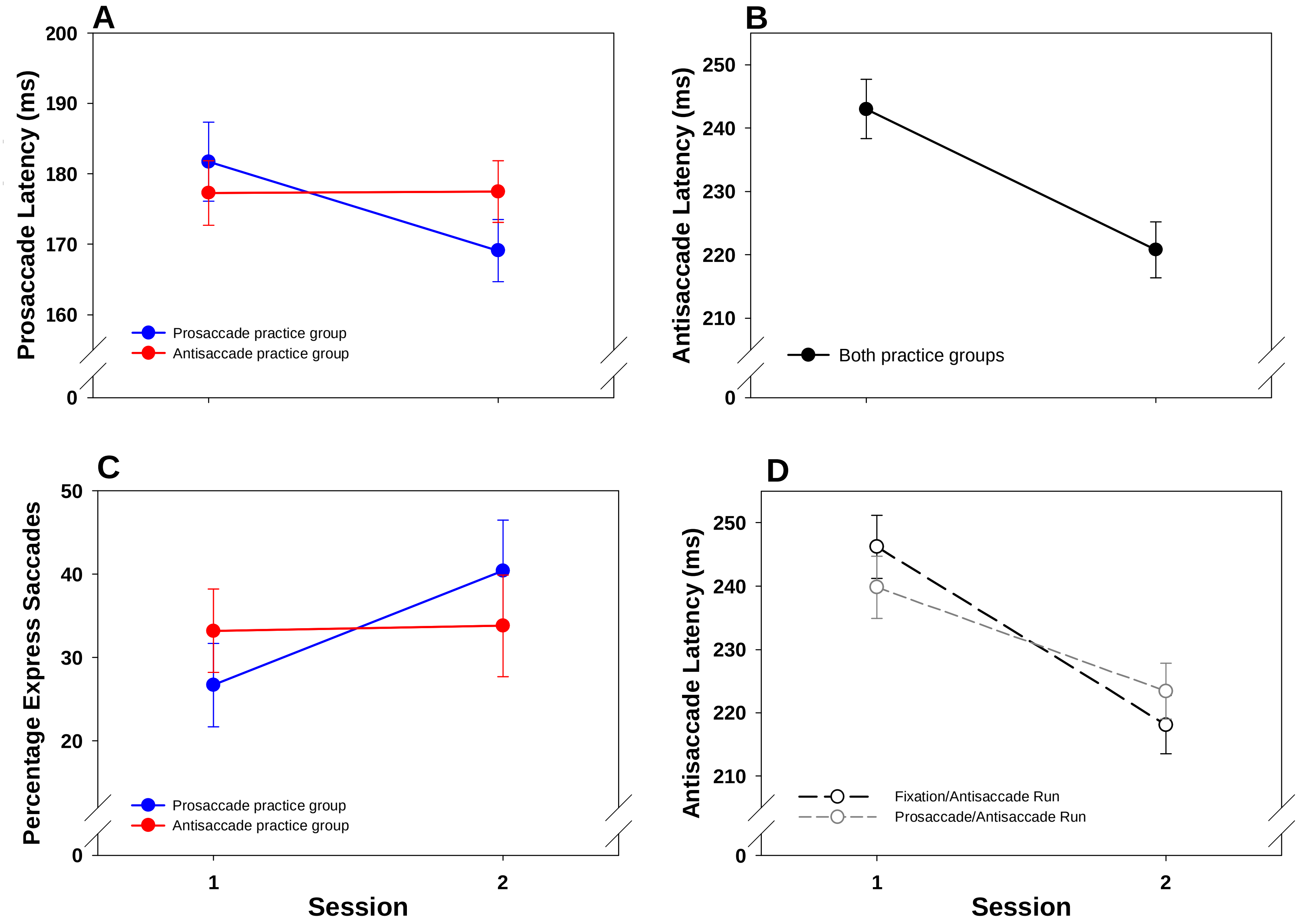
Means and Standard Errors for Significant Effects - FMRI

Region	Effect	Mean	Standard Error
Fixation/Prosaccade Run			
IFG	*Main Effect Session*		
	Session 1	.076	.025
	Session 2	.001	.022
IPL	*Main Effect Session*		
	Session 1	.082	.018
	Session 2	.031	.015
Fixation/Antisaccade Run			
R DLPFC	*Main Effect Session*		
	Session 1	.142	.020
	Session 2	.086	.023
IFG	*Main Effect Session*		
	Session 1	.161	.020
	Session 2	.067	.024
Cuneus	*Main Effect Session*		
	Session 1	.351	.023
	Session 2	.265	.028
Precuneus	*Group x Session*		
	Pro group, session 1	.286	.045
	Pro group, session 2	.327	.040
	Anti group, session 1	.329	.045
	Anti group, session 2	.254	.040
IPL	*Group x Session*		
	Pro group, session 1	.095	.014
	Pro group, session 2	.093	.019
	Anti group, session 1	.123	.014
	Anti group, session 2	.039	.019
ACC	*Group x Session*		
	Pro group, session 1	.042	.023
	Pro group, session 2	.057	.019
	Anti group, session 1	.128	.023
	Anti group, session 2	.047	.019



<u>Figure 4.1</u> Percent Correct Saccades – FMRI Sessions
Bar graph showing mean percentage of errors (and standard error) generated during prosaccades (blue bars) and antisaccades (red bars) during the FMRI sessions. For prosaccades, there was an effect of run type. The solid blue bar represents percent correct during the fixation/prosaccade run, and the hatched blue bar represents percent correct during the prosaccade/antisaccade run.

<u>Figure 4.2</u> Latency and Percent Express Saccades – FMRI Sessions
Line plots showing mean (a) prosaccade latency and (c) percent express prosaccades by practice group across fMRI sessions. The blue line represents the prosaccade practice group and the red line represents the antisaccade practice group. For antisaccade latency (b), there was no difference between groups, so data were collapsed across groups and are represented by a solid black line. For antisaccade latency (d) there was an effect of run type. The black dashed line represents latency during the fixation/antisaccade run and the gray dashed line represents latency during the prosaccade/antisaccade run.


A
Prosaccade Latency (ms)
200
190
180
170
160
0
Prosaccade practice group
Antisaccade practice group
B
Antisaccade Latency (ms)
250
240
230
220
210
0
Both practice groups
C
Percentage Express Saccades
50
40
30
20
0
Prosaccade practice group
Antisaccade practice group
1
2
Session
D
Antisaccade Latency (ms)
250
240
230
220
210
0
Fixation/Antisaccade Run
Prosaccade/Antisaccade Run
1
2
Session

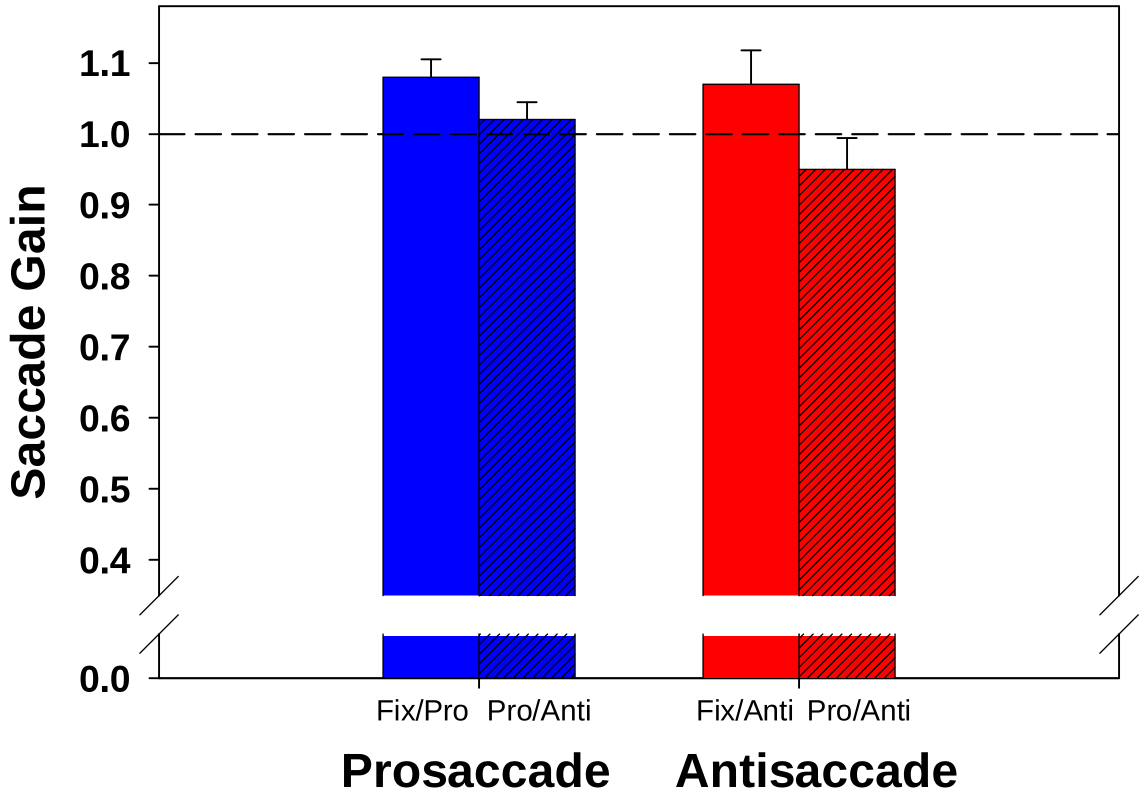
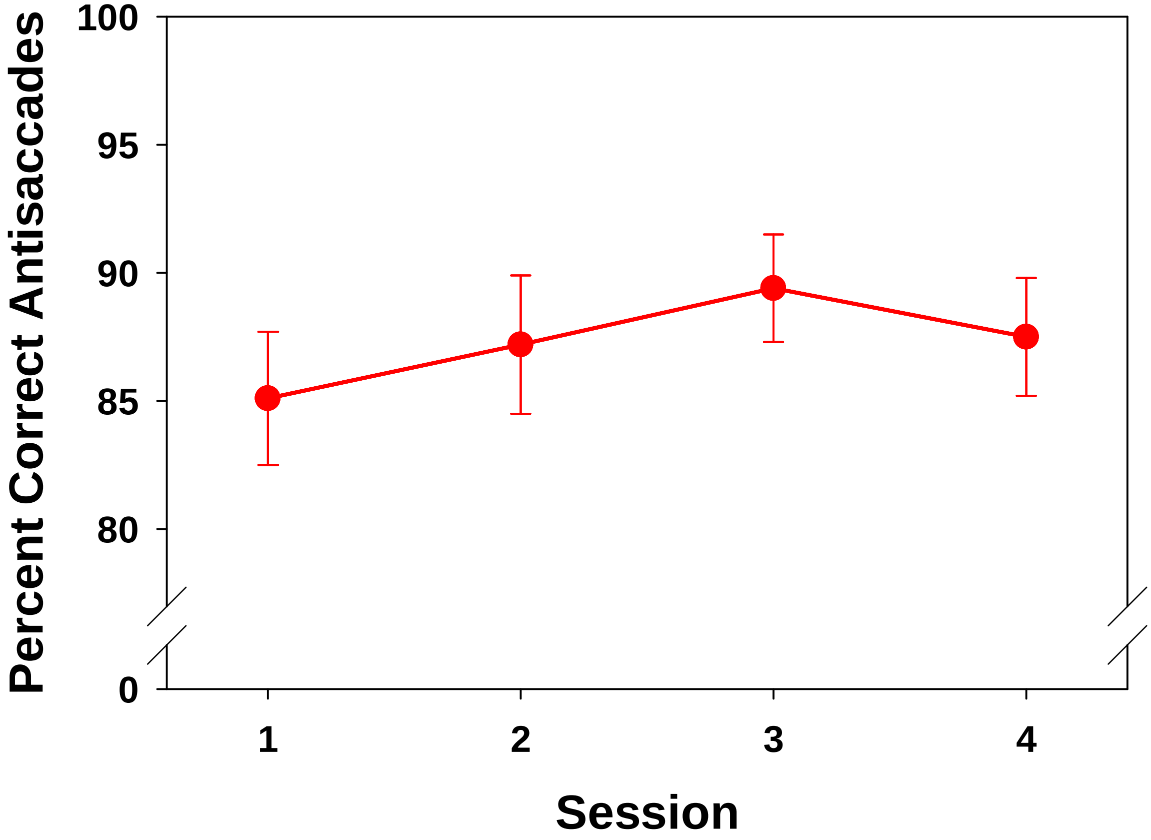
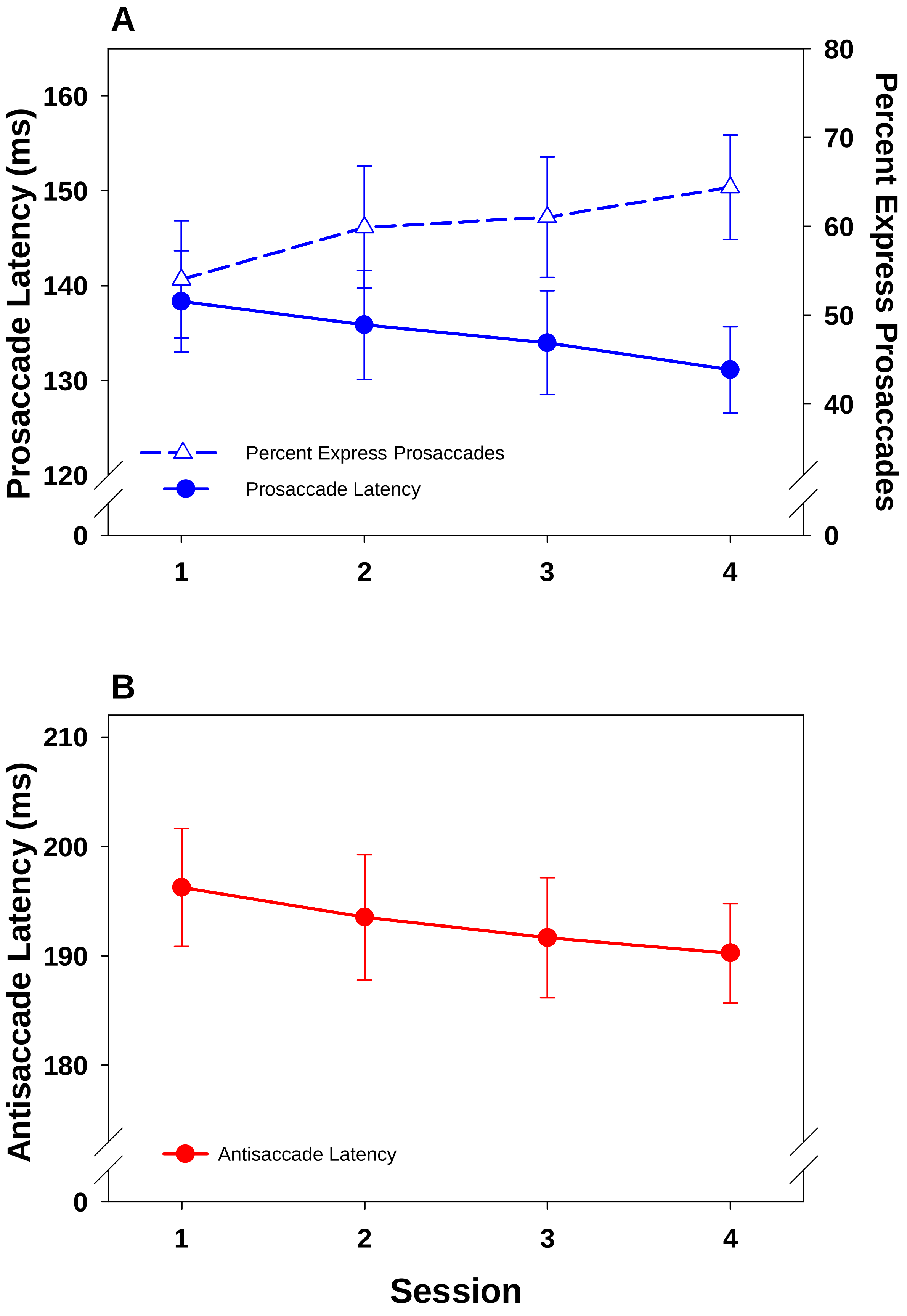


Figure 4.3 **Saccade Gain – FMRI Sessions**
Bar graph showing mean saccade accuracy (and standard error) during prosaccades (blue bars) and antisaccades (red bars) during the FMRI sessions. For both pro- and anti-saccades, there was an effect of run type. The solid bar represents saccade gain during the single task run, and the hatched bar represents saccade gain during the mixed saccade run. A score of 1.0 indicates perfect spatial accuracy. Values greater than 1.0 indicate saccades that overshoot the target and values less than 1.0 indicate saccades that undershoot the target.

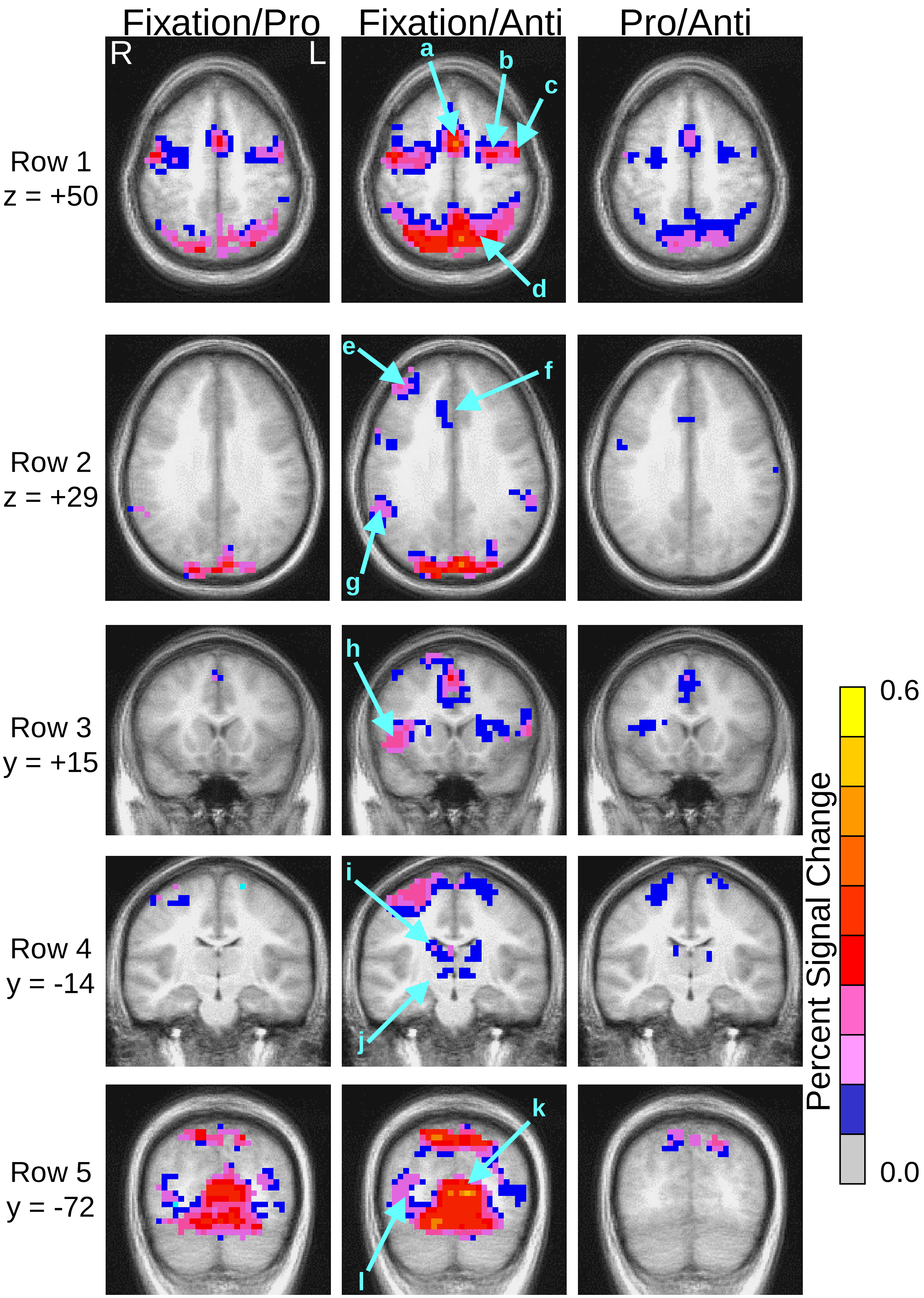


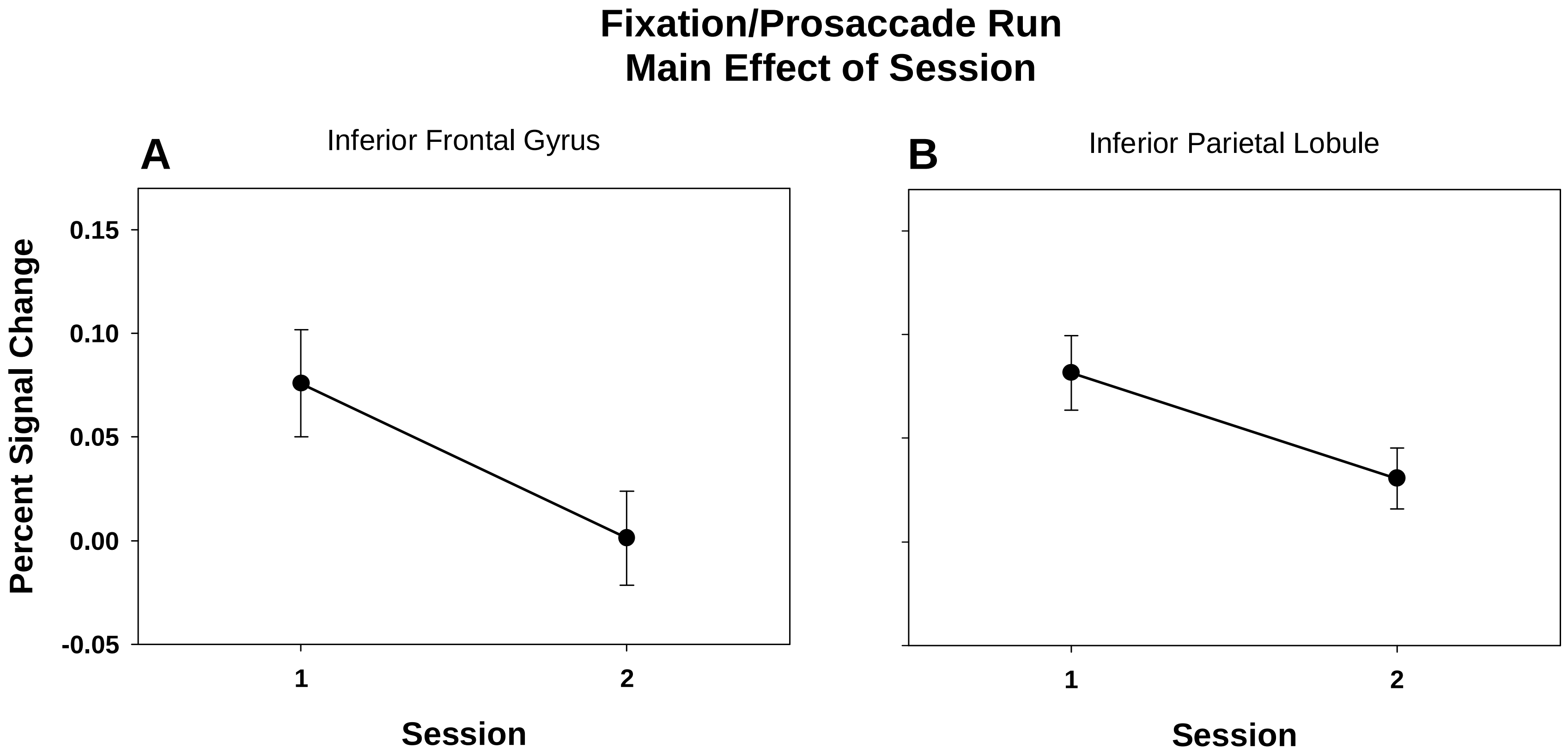
<u>Figure 4.4</u> Percent Correct Antisaccades – EEG Practice Sessions
Line plots showing mean (and standard error) percentage of correct antisaccades for the antisaccade practice group across EEG sessions.

<u>Figure 4.5</u> Latency and Percent Express Saccades – EEG Practice Sessions
Line plots showing mean (a) prosaccade latency (left axis, solid blue line) and percent express prosaccades (right axis, dashed blue line) for the prosaccade practice group across EEG sessions and mean (b) antisaccade latency for the antisaccade practice group across EEG sessions.


A
Prosaccade Latency (ms)
160
150
140
130
120
0
Percent Express Prosaccades
80
70
60
50
40
0
Percent Express Prosaccades
Prosaccade Latency
1
2
3
4
B
Antisaccade Latency (ms)
210
200
190
180
0
Antisaccade Latency
1
2
3
4
Session

<u>Figure 4.6</u> BOLD Activity Associated with Saccades
Axial views of one sample (N=32) t-maps representing percent signal change in BOLD contrast associated with the experimental condition at the first fMRI session for the three runs: (A) fixation/prosaccade, (B) fixation/antisaccade, and (C) prosaccade/antisaccade. The t-map for the fixation/antisaccade run was used to determine ROIs, which are denoted by lowercase letters a-l and are listed in Table 4.1 . The maps are overlaid on an average structural map of 21 subjects. Figures are shown using radiological convention (left hemisphere on right side).


Fixation/Pro
Fixation/Anti
Pro/Anti
R
L
a
b
c
d
e
f
g
h
i
j
k
l
Row 1
z = +50
Row 2
z = +29
Row 3
y = +15
Row 4
y = -14
Row 5
y = -72
0.6
0.0
Percent Signal Change



<u>Figure 4.7</u> Fixation/Prosaccade Run – Main Effect of Session (FMRI)
Line plots showing decreases in prosaccade-related BOLD signal across FMRI sessions in (a) inferior frontal gyrus and (b) inferior parietal lobule. Black dots represent mean percent signal change from baseline at each session.

<u>Figure 4.8</u> Fixation/Antisaccade Run – Main Effect of Session (FMRI)
Line plots showing decreases in antisaccade-related BOLD signal across FMRI sessions in (a) right dorsolateral prefrontal cortex (b) inferior frontal gyrus and (c) cuneus. Black dots represent mean percent signal change from baseline at each session.

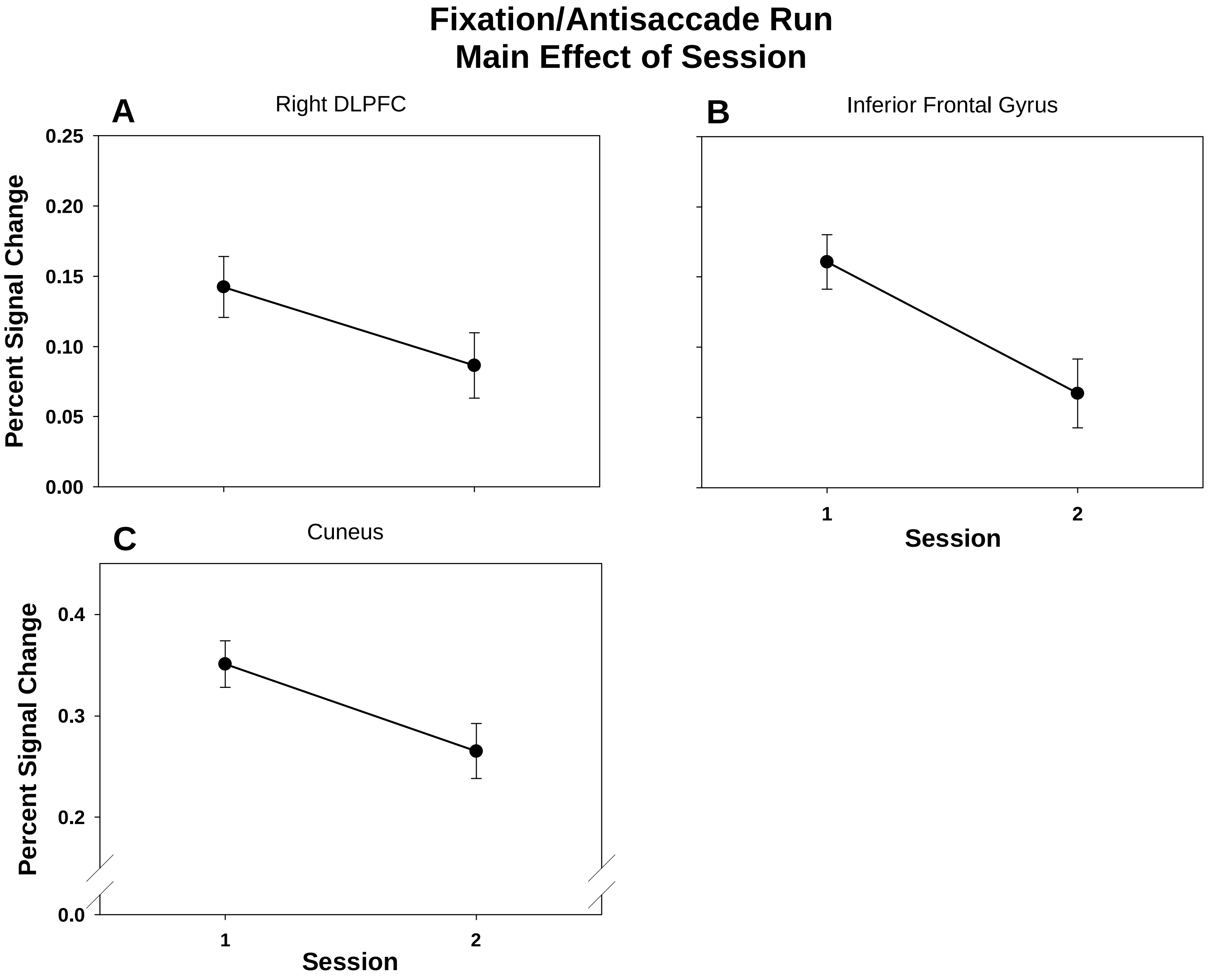
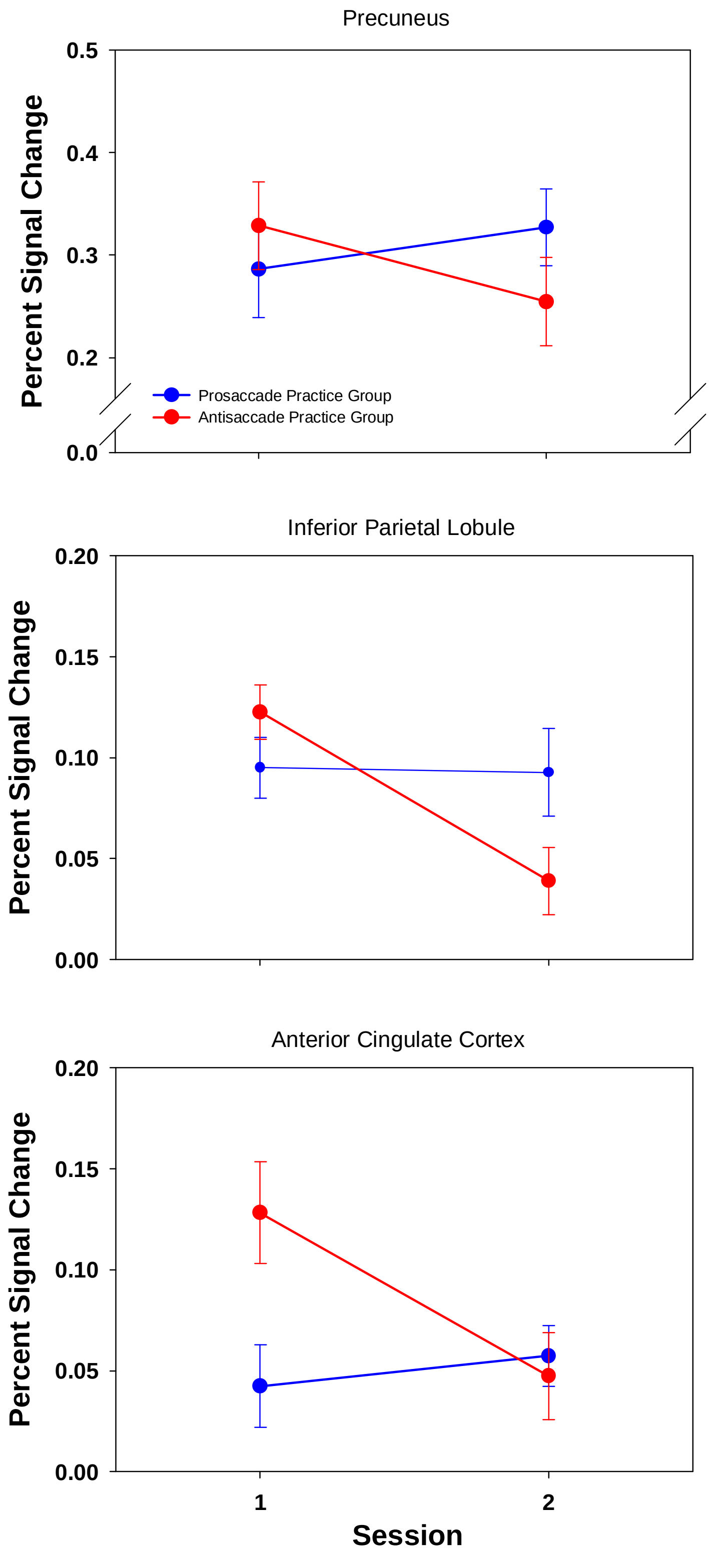

Fixation/Antisaccade Run
Main Effect of Session
A
Right DLPFC
0.25
0.20
0.15
0.10
0.05
0.00
Percent Signal Change
B
Inferior Frontal Gyrus
1
2
Session
C
Cuneus
0.4
0.3
0.2
0.0
Percent Signal Change
1
2
Session

Figure 4.9 **Fixation/Antisaccade Run – Group x Session Effects (FMRI)**
Line plots showing decreases in antisaccade-related BOLD signal by practice group across FMRI sessions in (a) precuneus (b) inferior parietal lobule and (c) anterior cingulate cortex. Blue dots and lines represent the prosaccade practice group. Red dots and lines represent the antisaccade practice group.

Fixation/Antisaccade Run Group x Session Interaction



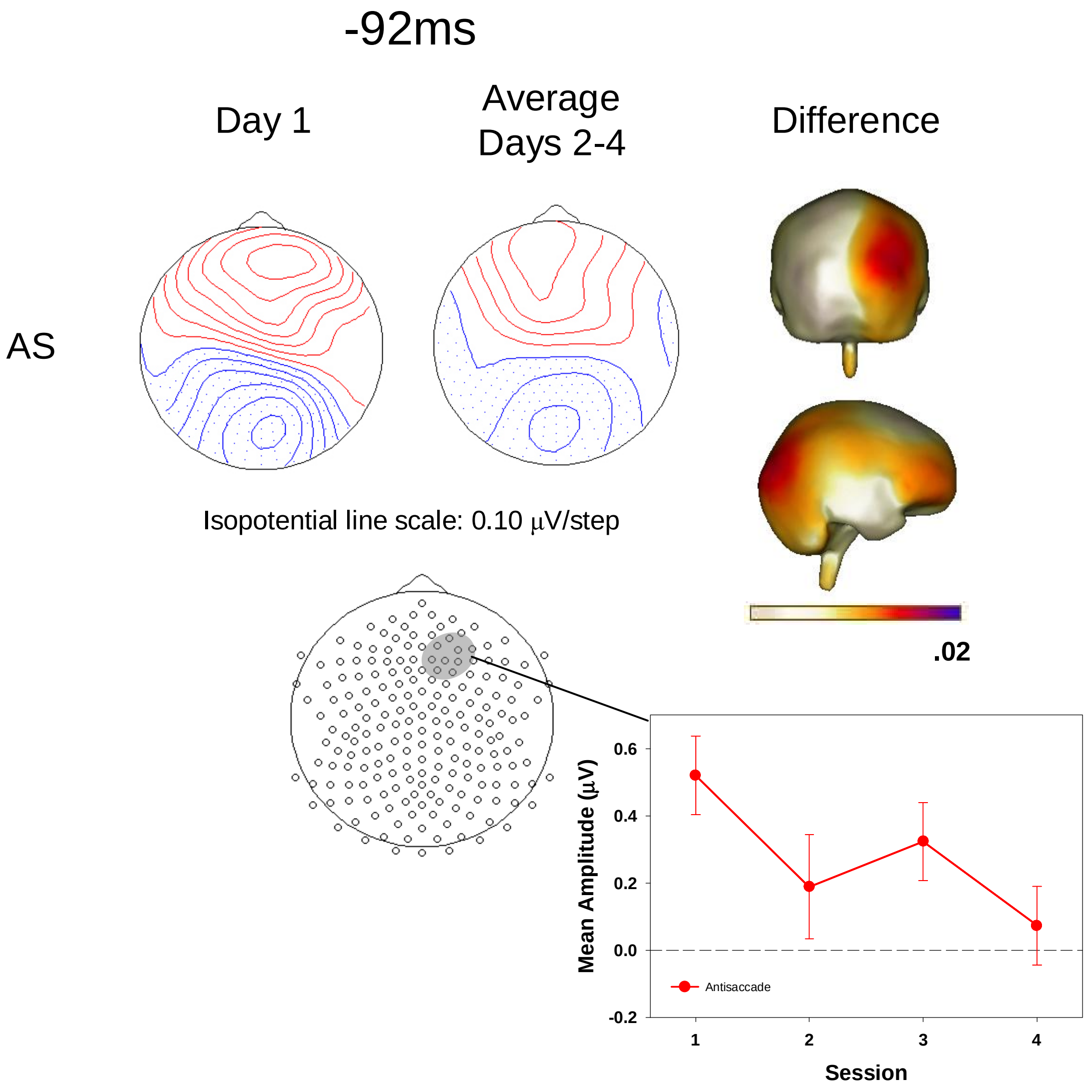


Figure 4.10 Antisaccade Gap Period (EEG)
Top-down meridian maps of scalp potentials at 92 ms prior to stimulus onset (-92ms) for antisaccades at EEG Session 1 and the average of Sessions 2-4. Positive isopotential lines are in red, negative isopotential lines are in blue. Clusters of sensors within which significant ANOVA results were found are indicated by gray areas on top of the sensor map. The line graph shows the absolute mean potential amplitudes (with standard errors) averaged over sensors within the cluster. Minimum norm estimation maps of the difference between Session 1 and the average of Sessions 2-4 are shown to the right of the potential maps.

Figure 4.11 **Prosaccade Gap Period (EEG)**
A) Top-down meridian maps of scalp potentials at 92 ms prior to stimulus onset (-92ms) for prosaccades at EEG Session 1 and the average of Sessions 2-4. Positive isopotential lines are in red, negative isopotential lines are in blue. Clusters of sensors within which significant ANOVA results were found are indicated by gray areas on top of the sensor map. The line graph shows the absolute mean potential amplitudes (with standard errors) averaged over sensors within the cluster. Minimum norm estimation maps of the difference between Session 1 and the average of Sessions 2-4 are shown to the right of the potential maps.
B) Top-down meridian maps of scalp potentials at 92 ms prior to stimulus onset (-92ms) for regular prosaccades and express prosaccades. The bar graphs show the absolute mean potential amplitudes (with standard errors) averaged over sensors within the cluster. Minimum norm estimation maps of the difference between regular and express prosaccades are shown to the right of the potential maps.

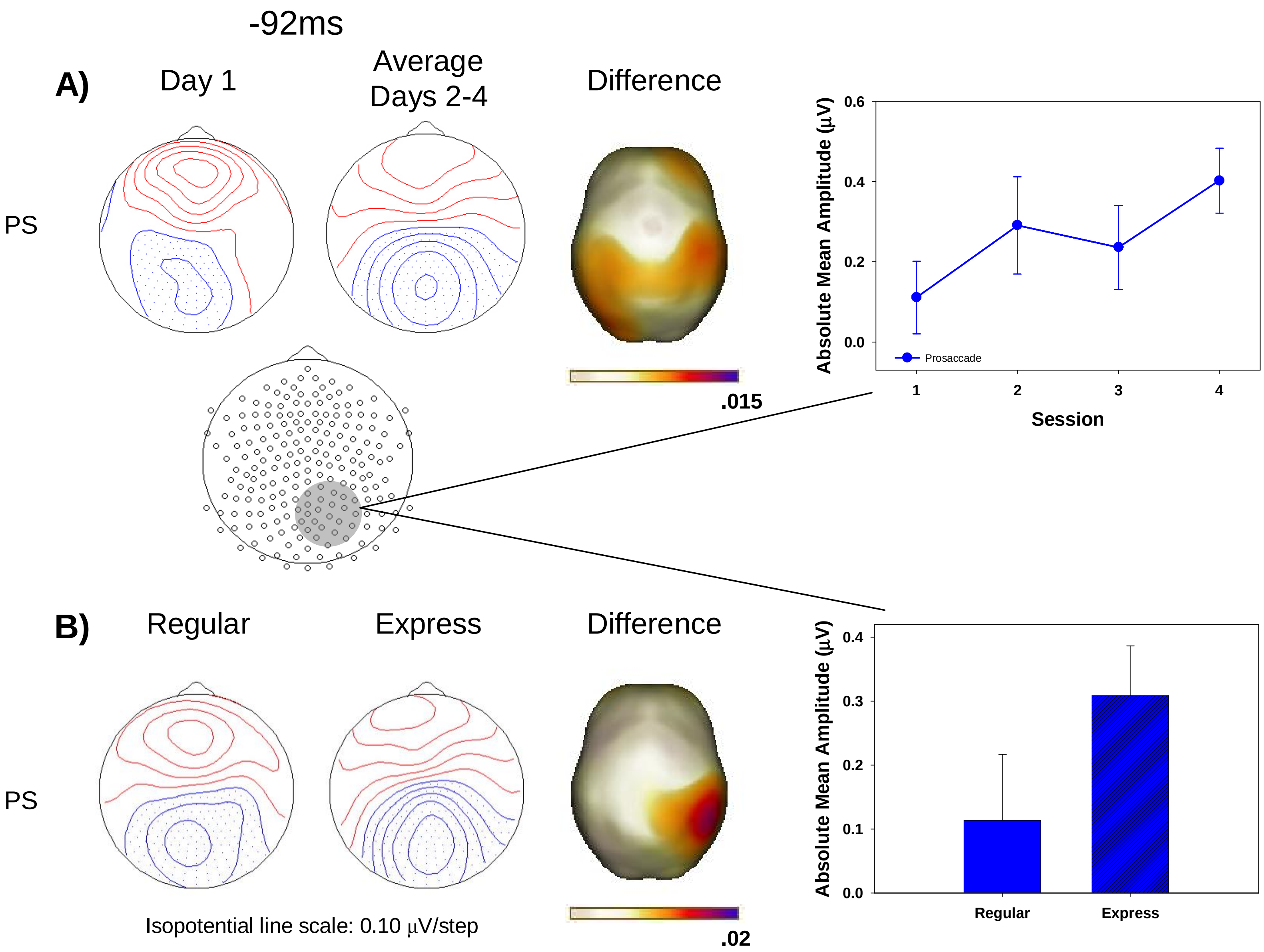
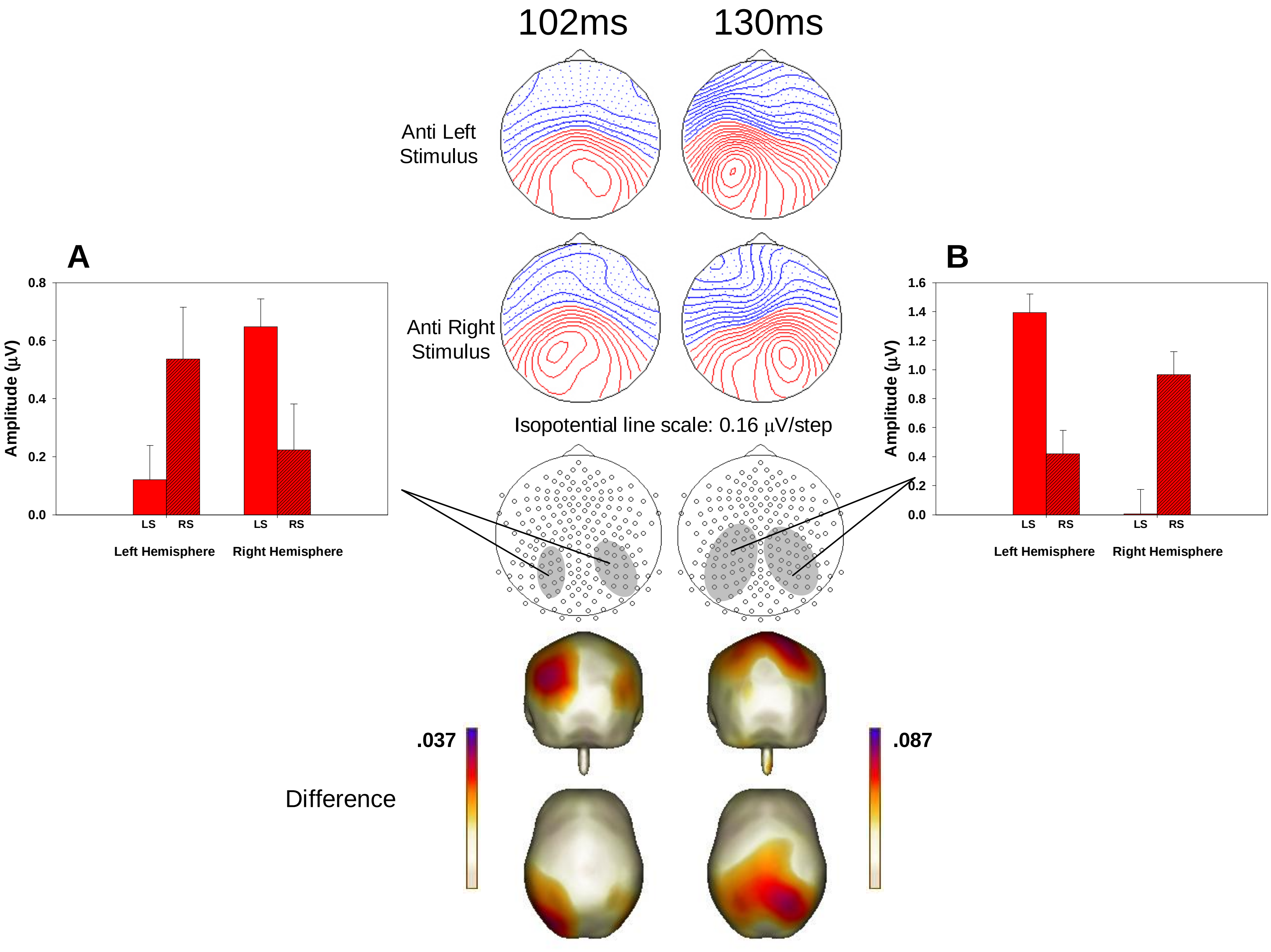

-92ms
A)
Day 1
Average Days 2-4
Difference
PS
.015
Absolute Mean Amplitude (μV)
0.6
0.4
0.2
0.0
Prosaccade
1
2
3
4
Session
B)
Regular
Express
Difference
PS
Isopotential line scale: 0.10 μV/step
.02
Absolute Mean Amplitude (μV)
0.4
0.3
0.2
0.1
0.0
Regular
Express

Figure 4.12 **Antisaccade Stimulus Registration and Vector Inversion (EEG)**
Top-down meridian maps of scalp potentials at a) 102 ms and b) 130 ms after stimulus onset for antisaccades with left stimuli and antisaccades with right stimuli. Positive isopotential lines are in red, negative isopotential lines are in blue. Clusters of sensors within which significant ANOVA results were found are indicated by gray areas on top of the sensor map. The bar graphs shows the absolute mean potential amplitudes (with standard errors) averaged over sensors within each cluster. Minimum norm estimation maps of the difference between antisaccades with left and right stimuli are shown below the potential maps.


102ms
130ms
Anti Left Stimulus
Anti Right Stimulus
Isopotential line scale: 0.16 μV/step
A
0.8
0.6
0.4
0.2
0.0
Amplitude (μV)
LS
RS
LS
RS
Left Hemisphere
Right Hemisphere
B
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Amplitude (μV)
LS
RS
LS
RS
Left Hemisphere
Right Hemisphere
.037
.087
Difference

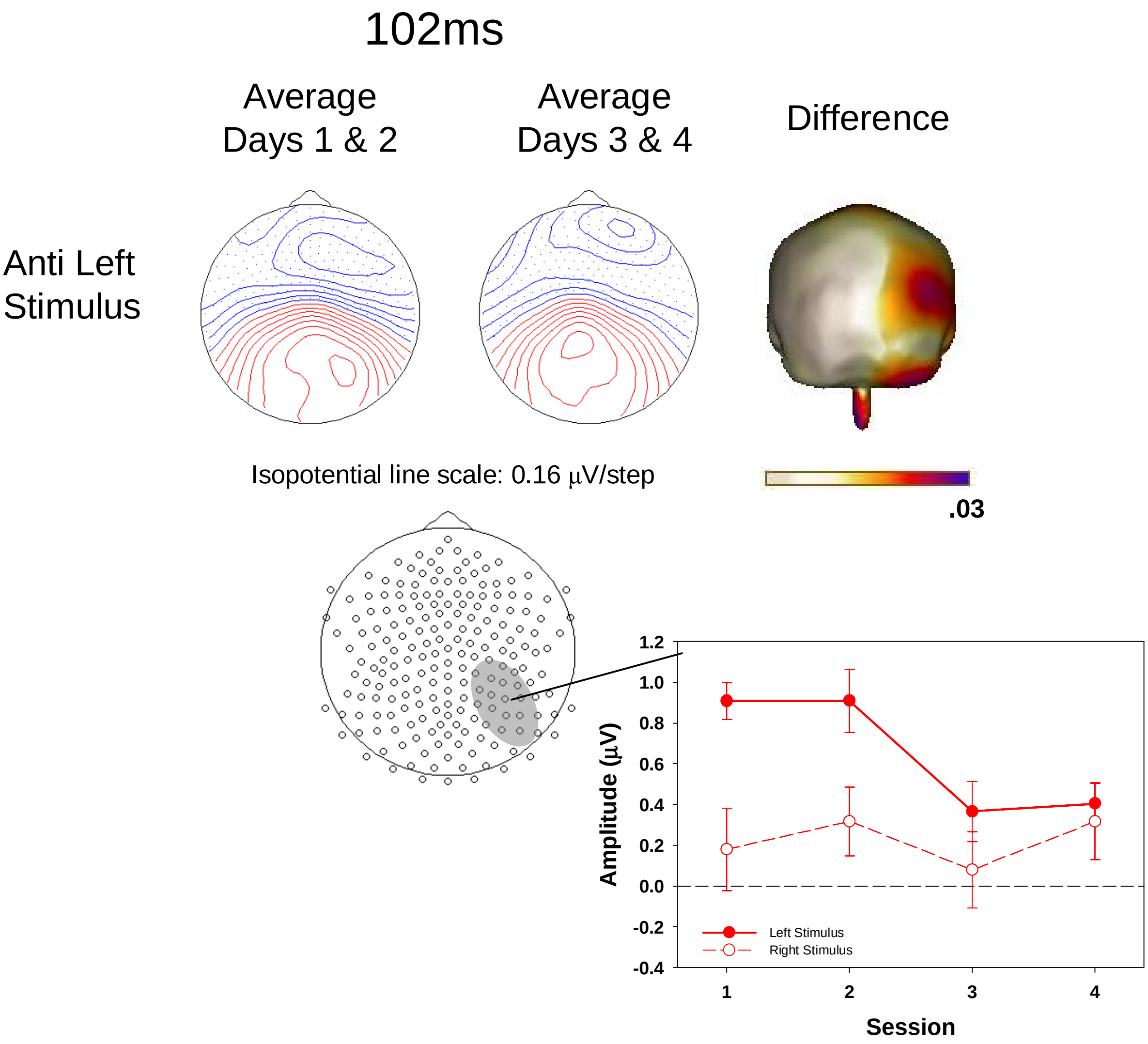


Figure 4.13 **Antisaccade Stimulus Registration – Main Effect of Session (EEG)**
Top-down meridian maps of scalp potentials at 102 ms after stimulus onset for antisaccades with left stimuli for the average of EEG Sessions 1-2 and the average of Sessions 3-4. Positive isopotential lines are in red, negative isopotential lines are in blue. Clusters of sensors within which significant ANOVA results were found are indicated by gray areas on top of the sensor map. The line graph shows the absolute mean potential amplitudes (with standard errors) averaged over sensors within the cluster. Minimum norm estimation maps of the difference between the average of Sessions 1-2 and the average of Sessions 3-4 are shown to the right of the potential maps.

CHAPTER 5

DISCUSSION

The present study examined changes in behavior and brain activity during and after the practice of pro- and anti-saccade tasks. FMRI was used to investigate the strength of activity in saccade circuitry during both prosaccades *and* antisaccades for all participants at two points: before and after one week of practice. Between FMRI sessions, participants practiced either prosaccades *or* antisaccades daily while EEG data were recorded, which allowed for the examination of changes in the spatial distribution and timing of activity over the course of the individual practice sessions. It was expected that practice would result in improved performance on the practiced task and decreased brain activity, reflecting changes in the amount of cognitive control necessary to perform the task and greater efficiency within specific regions of the task-related neural circuitry. Thus, changes in behavior and brain activity should be dependent upon the type of saccade practiced. In this section, behavior changes will be discussed first, followed by changes observed in the EEG practice sessions, and then changes observed in the fMRI sessions. Finally, in a concluding section, a general discussion will synthesize the main findings of the study.

Behavioral Measures

The percent of correct prosaccades did not differ across fMRI sessions for either group and did not differ across practice sessions for the prosaccade practice group. As is typical, participants made few prosaccade direction errors (less than 2% of trials). Thus, there is little room for improvement on this task. In the present study, participants performed prosaccades under two conditions: alternating with fixation, and alternating with antisaccades. Although participants rarely err in either context, there is evidence that performing prosaccades in a mixed saccade paradigm increases error rate, at least for the first prosaccade after a string of antisaccades (Dyckman et al., 2007). Consistent with this finding, in the fMRI scanner, participants in the present study made more prosaccade errors during the prosaccade/antisaccade run than during the fixation/prosaccade run. During EEG practice sessions, the prosaccade practice group trained on the fixation/prosaccade run, not the prosaccade/antisaccade run; it would be interesting to investigate whether practicing prosaccades in a mixed saccade context would eliminate this difference.

Prosaccade latency decreased across fMRI sessions for the group that practiced the prosaccade task, consistent with previous studies (Dyckman & McDowell, 2005; Fischer & Ramsperger, 1986). This group also made more express saccades, the very fast saccades with reaction times between 90ms and 135ms, at the second fMRI session. Participants in this group showed steady improvements in latency and percentage of express saccades across practice sessions in the EEG environment. This effect is attributable to practice, as the group that practiced antisaccades between fMRI sessions had prosaccade latencies and percent of express saccades that were the same across fMRI sessions. The decrease in prosaccade latency for the prosaccade practice group and the stability of prosaccade latency for the antisaccade practice group is identical to the results of Dyckman and McDowell (2005).

Similar to Dyckman et al. (in preparation), neither group showed a change in the percentage of correct antisaccades from one fMRI session to the next. The antisaccade practice group, however, did show significant changes in percent correct across individual practice sessions. Participants improved their performance from the first session to the third session, with no further significant change to the fourth practice session. Had performance not been recorded during practice sessions, this behavioral trend would have been missed and only the lack of change in percent correct from one fMRI session to the next would have been observed. It was expected that the antisaccade practice group would improve their performance throughout the practice period and into the second fMRI session, but this was not the case. The reason for the initial improvement followed by a decline back to the pre-practice level is unclear. It could be that participants are beginning to invoke a new strategy to perform the antisaccade task and more practice would result in consolidation of this strategy, similar to Hempel et al. (2004). It is also possible that participants did not receive enough practice to result in sustained improvement in the percentage of correct antisaccades. Future studies might benefit from tailoring the amount of practice to individual participants. For example, participants could be trained until they reach a criterion level of performance or they could be tested using a dual-task paradigm to check for automaticity of the task, as in Poldrack et al. (2005).

Both groups decreased their latencies to correct antisaccades from the first fMRI session to the second fMRI session. The antisaccade practice group also showed a steady decrease in latency across EEG practice sessions. While the prosaccade group did not practice antisaccades between fMRI sessions, their decreased antisaccade latency at the second fMRI session was not completely unexpected, as it is consistent with the results of Dyckman and McDowell (2005). All participants were naïve to antisaccades prior to the first fMRI session, and as such, this session likely served as practice for the second fMRI session, as in Ettinger et al. (2003), regardless of the saccade tasks practiced between fMRI sessions.

The context in which antisaccades were performed affected the rate of decrease in antisaccade latency from the first to the second fMRI session. Latency decreased to a greater extent for the fixation/antisaccade run compared to the prosaccade/antisaccade run. The prosaccade/antisaccade run is more difficult than the fixation/antisaccade run. Evidence comes from the fact that a greater proportion of errors are generated on pro-saccade trials that follow anti-saccade trials (Cherkasova et al., 2002; Dyckman et al., 2007). Alternating pro- and anti-saccades increases working memory to maintain task instructions and increases the complexity of response selection since the correct response in one block is the incorrect response on the next block. Thus, the same amount of practice may not have as great an effect on this task. Furthermore, neither group practiced the prosaccade/antisaccade run; the antisaccade practice group practiced the fixation/antisaccade run only, and although not significant, the antisaccade practice group showed a larger latency decrease across sessions than the prosaccade practice group.

Spatial accuracy on both tasks remained stable across test sessions for both groups. For the prosaccade task, participants were slightly more accurate during the mixed saccade run compared to the single saccade run, but in both contexts, spatial accuracy was excellent, missing the target location by only about 5% of the total distance from central fixation. For the antisaccade task, participants tended to make saccades past the target location during the fixation/antisaccade run, but tended to make saccades that didn’t quite reach the target location during the mixed saccade run. Again, saccades in both contexts were highly accurate (missing the target location by around 5%).

Changes Across EEG Practice Sessions

Each group showed changes in brain activity associated with their practiced task across the practice sessions. With EEG, it was possible to examine preparatory activity that occurred prior to the appearance of a peripheral stimulus. There was significant activity during the gap period that preceded stimulus onset for both prosaccades and antisaccades, and changes in gap period activity across sessions were evident for both tasks.

Two theories regarding the mechanism by which a temporal gap decreases saccade latency have been discussed in the literature. One theory posits that fixation offset disinhibits the movement cells in superior colliculus, and thus, once a peripheral target is presented, a saccade can be generated quickly. Dorris and Munoz (1995) found neurophysiological evidence to support this “sensory-driven” explanation for the gap effect. They recorded from fixation cells within superior colliculus and observed that the minimal discharge rate for fixation cells occurred approximately 200-300 ms after fixation offset, which corresponds to the length of the gap period (200ms) that results in the maximum reduction in saccade latency (McDowell & Clementz, 1997; Fischer & Weber, 1997).

In a study using fMRI, Neggers et al. (2005) observed an increase in activity in superior colliculus for gap saccade trials compared to regular saccade trials. The authors suggest that this increased activity is the result of disinhibition of the entire motor map within the superior colliculus, in preparation for a saccade. Low superior colliculus activity during regular saccade trials, then, would be due to activation of the fixation neurons, of which there are considerably fewer. A negative correlation between superior colliculus activity and reaction time supports this interpretation. Increased activity in superior colliculus was associated with decreased saccadic reaction times.

In the second theory, the gap effect is explained by a “top-down” mechanism, the disengagement of attention on the fixated stimulus, which facilitates a saccade toward a peripheral stimulus. A recent behavioral study by Pratt et al. (2006) modulated attention to the fixation stimulus to determine whether attention plays a role in the gap effect. Participants were instructed to pay attention to one of two lines of an “X” that made up the center fixation stimulus. Latencies were recorded when either the attended line or the unattended line were removed prior to peripheral stimulus onset. Saccade latencies were faster when the attended line was removed than when the unattended line was removed, suggesting that attentional modulation contributes to the gap effect. The mechanism by which the disengagement of attention facilitates faster saccades is unknown; however, it is possible that the two theories are actually two components of one larger theory. Attentional disengagement may modulate cell firing in the superior colliculus, either by inhibiting the fixation cells or disinhibiting the movement cells (Pratt et al., 2006).

Results from the present study are consistent with a top-down explanation of the gap effect, although they do not rule out a stimulus-driven component. For prosaccades, there was significant activity 100 ms before stimulus presentation (about 100 ms into the gap period) in parietal cortex, a region associated with visual attention. The increase in activity in this region with practice occurred in conjunction with decreased latencies and an increase in the percentage of express saccades, suggesting that increased parietal cortex activity during the gap period may facilitate express saccades. This is supported by the fact that there was greater activity in right parietal cortex during the same time period prior to generation of express saccades than prior to generation of regular saccades.

For antisaccades, the sources of activity during this time period included right occipital/parietal cortex, but also included an area of right frontal cortex. Activity in these regions decreased across practice sessions, possibly to decrease the likelihood of generating erroneous prosaccades toward the cue. If top-down signals during the gap period serve to disengage attention and/or inhibit fixation cells in superior colliculus, as described above, a decrease in activity in these regions would be advantageous for antisaccades. Maintaining attention on the location of the fixation stimulus, even when it disappears may help to avoid glancing toward the peripheral stimulus.

The period after stimulus presentation was also examined for antisaccades. Specifically, activity in visual cortex (associated with stimulus registration) and activity in parietal cortex (associated with saccade vector inversion) were investigated. As expected, activity in contralateral visual cortex was observed in response to the presentation of the visual stimulus. The peak of this activity was approximately 100 ms after stimulus presentation. Following this peak, a second peak of activity was observed about 130 ms after stimulus presentation. Source analysis at this timepoint revealed that the source of this activity was in parietal cortex ipsilateral to the visual stimulus. Thus, activity in response to a visual stimulus began in *contralateral visual cortex*, then switched to parietal cortex, *ipsilateral to the stimulus*, but *contralateral to the saccade location*. This result is consistent with the role of posterior parietal cortex in performing the vector inversion necessary to generate a correct antisaccade to the mirror image location of a peripheral cue (Everling et al., 1998; Medendorp et al., 2005; Moon et al., 2007; Zhang & Barash, 2000).

Activity in visual cortex 100ms after stimulus presentation was also examined to determine whether practice of antisaccades affects early visual activity. Foxe and Simpson (2002) suggest that visual cortex activity around 100ms after stimulus presentation is not simply sensory driven, but also reflects top-down influences, primarily from frontal and parietal regions. Hahn et al. (2006) also found middle occipital gyrus to be receptive to top-down influences at this early stage of processing, and Poghosyan et al. (2005) observed that visual cortex was strongly modulated by attention during the same time period. Thus, it was hypothesized that, with practice, early activity in visual cortex contralateral to the stimulus would decrease due to less investment in the peripheral stimulus in order to facilitate looking away from it. Results for right visual cortex are consistent with this hypothesis. For stimuli in the left visual field, activity in right visual cortex at approximately 102ms after stimulus presentation decreased with practice, most notably from the second practice session to the third. Attention modulation of visual cortex activity may explain why some studies have found greater activity in middle occipital gyrus for prosaccades than for antisaccades (Dyckman et al., 2007; McDowell et al., 2005). With practice, participants may further decrease their attention to the peripheral stimulus as a strategy to improve performance, which would be reflected in the strength of activity in visual cortex.

Changes Across FMRI Sessions

Prosaccade-Related Activity

Decreased Prosaccade-Related Activity over Time for Both Groups

Participants showed decreases in prosaccade-related brain activity in two regions, regardless of which type of saccade they practiced. The group that practiced prosaccades, however, also had shorter latencies and more express prosaccades at the second fMRI session. Thus, the prosaccade practice group increased their performance and showed decreased activity in the circuitry supporting performance, while the antisaccade practice group showed decreased activity, while maintaining the same level of performance.

Prosaccade-related activity in inferior frontal gyrus (IFG) decreased across time for participants as a whole. This area, while generally associated with inhibition (e.g. Aron & Poldrack, 2006; Aron et al., 2004; Chambers et al., 2006) is also associated with executive function, including working memory and task switching (e.g. Buchsbaum et al., 2005). The prosaccade task was not expected to require activity in regions associated with cognitive control, and thus, decreased activity in this region after practice were not expected. The low level of activity in IFG during the fixation/prosaccade run at the first fMRI session, however, may reflect the maintenance of task instructions for the fixation and prosaccade blocks. Activity in this region dropped to almost zero at the second fMRI session, possibly due to a reduced working memory load after some experience with the tasks. This pattern of results coupled with the fact that IFG has not previously been associated with prosaccades, suggests that IFG may be part of the "scaffolding" network necessary when a task is novel, but that this region is not specifically involved in prosaccade generation.

The second region showing decreased prosaccade-related activity from the first fMRI session to the second was inferior parietal lobule (IPL). This region is associated with spatial orienting and attentional control (Connolly et al., 2000; Hahn et al., 2006; Poghosyan et al., 2005). Hahn et al. (2006) observed the greatest activity in this region during a situation in which participants were able to predict where a relevant target was likely to appear, suggesting a role for inferior parietal lobule in endogenous orienting. If participants had to rely solely on the appearance of the target, with no prior information about where it would appear, IPL activity was significantly reduced. Decreased activity in this region at the second test session may have been the result of a decreased reliance on endogenous orienting, in favor of exogenous, stimulus-driven orienting, which results in correct performance on the prosaccade task. A second possibility is that after practicing saccades to one of two peripheral locations, participants were able to attend to these locations more efficiently.

Antisaccade-Related Activity

All changes in antisaccade-related activity were observed for the fixation/antisaccade run. There were no changes in any regions of the saccade circuitry during the prosaccade/antisaccade run. There were two main categories of results for the effect of practice on antisaccade-related brain activity. First, there were three regions in which participants showed decreases in antisaccade-related activity regardless of practice group. Second, there were three regions in which only participants who practiced antisaccades showed decreases in antisaccade-related activity over time.

Decreased Antisaccade-Related Activity over Time for Both Groups

Right dorsolateral prefrontal cortex (DLPFC) was one of the regions that showed decreased activity across sessions for both practice groups. This result is consistent with the previous study by Dyckman et al. (in preparation), and thus was in line with one of the predictions made about this region. An alternative hypothesis was that only the antisaccade group would show a decrease in activity in this region as DLPFC is thought to be involved in the inhibition of the initial saccade toward the stimulus and only the antisaccade group would have practiced this aspect of antisaccade generation. As previously stated, however, both groups were naïve to the antisaccade task at the first test session, and therefore, increased DLPFC activity during the first session may be due, in part, to the working memory and response selection demands of the task (Bunge, 2004; Curstis & D’Esposito, 2003a). By the time of the second test session, all participants had already performed the task at least once and therefore, they may have required less cognitive control to maintain task instructions and select the appropriate response. A prefrontal cortex mediated “scaffolding” network (Petersen et al., 1998) necessary to support novel tasks may not be necessary at the second test session.

While a decrease in cognitive control at the second fMRI session may explain why all participants showed a decrease in antisaccade-related DLPFC activity, it seems as though the antisaccade practice group should also have shown a specific task related decrease in DLPFC activity across sessions. If this were the case, the antisaccade practice group should have shown a larger decrease in PFC activity than the prosaccade group. In examining the patterns of change in right DLPFC for the two groups, the antisaccade group does show a steeper decrease in activity from the first to the second fMRI session. This interaction, however, did not reach significance.

Inferior frontal gyrus showed the same pattern of activity as right DLPFC. Activity in IFG has been associated with inhibition in a number of recent fMRI studies (e.g. Aron & Poldrack, 2006: Aron et al., 2004; Chambers, et al., 2006), and recently, activity in this area has also been observed specifically during antisaccades (Chikazoe et al., 2007; Dyckman et al., 2007), suggesting this region may be involved in the inhibitory aspect of the anti-saccade task. Activity in this region decreased across fMRI sessions for both groups. Like right DLPFC, however, this decrease was steeper for the antisaccade practice group, although the interaction was not significant.

When using a task where the brain regions supporting task performance are the same regions that underlie cognitive control (see Buchsbaum et al., 2005 for a review), it may be difficult to isolate the effects of decreased cognitive control from the effects of increased efficiency in the specific task circuitry. Both DLPFC and IFG were found to be common to both tasks of executive function and tasks requiring response inhibition in a meta-analysis by Buchsbaum et al. (2005). In both of these regions, there was a trend toward a greater decrease in activity for the antisaccade practice group, and both regions still showed significant antisaccade-related activity after practice, suggesting their involvement in the antisaccade task is not limited to general executive function, such as maintaining task instructions.

The third region that showed a decrease in activity across participants after practice is the cuneus. This region is associated with volitional saccade performance and sensorimotor integration, specifically integrating information from the retina with the command to make an eye movement (O’Driscoll et al., 2000; Shipp et al., 1998). Cuneus may also be one of the regions that influences early visual areas (McDowell et al., 2005; Vanni et al., 2001). All participants practiced saccades between the first and second test sessions; both prosaccades and antisaccades require the transformation of a sensory signal into a motor command. As such, the stimulus-response pairing may have been strengthened, resulting in a more efficient circuit and decreased activity in this region at the second fMRI session.

Decreased Antisaccade-Related Activity over Time for the Antisaccade Practice Group Only

Regions showing a decrease for the antisaccade group only suggest that, in addition to a decrease in cognitive control after practice, there is a decrease in regions specifically associated with antisaccade performance. In precuneus, an area in posterior parietal cortex, the antisaccade practice group shows decreased activity across time while the prosaccade group shows increased activity across time. This result is in line with the hypotheses of the study and is similar to the result observed by Dyckman et al. (in preparation). Precuneus is thought to be associated with sensorimotor transformation and the vector inversion necessary to generate a correct antisaccade (e.g. Medendorp et al., 2005; Moon et al., 2007). The EEG results of the current study are also consistent with the role of posterior parietal cortex in vector inversion, although the spatial resolution of the EEG data does not allow for the precise identification of the region as precuneus. The antisaccade group was able to practice this vector inversion throughout the week, especially because the visual angle of the stimuli was the same for practice and test sessions. The prosaccade group, on the other hand, did not have to perform vector inversion during their practice sessions because their saccades were made to visual stimuli. Thus, it seems as though practice of this aspect of antisaccade generation resulted in the need for less activity in the precuneus region to perform at the same level. On the other hand, practicing the prosaccade task, where the cue is the same as the saccade target, may have resulted in a greater need for precuneus activity to accurately generate an antisaccade to the mirror image location of the cue.

The antisaccade practice group also showed decreased activity across fMRI sessions in inferior parietal lobule. Interestingly, each practice group showed a decrease in activity in this region for their practiced task. The antisaccade practice group, however, also showed decreased activity for the unpracticed prosaccade task. As mentioned previously, IPL is thought to be involved in attentional control. The antisaccade task may require greater attentional control than the prosaccade task, and indeed, greater activity was observed in this region for antisaccades compared to prosaccades in the present study and others (e.g. Dyckman et al., 2007). Thus, the antisaccade practice group may have been able to apply their improved attentional control to the less demanding prosaccade task, while the prosaccade practice group was not able to transfer their learning to the antisaccade task.

The final region that showed decreased activity for the antisaccade group only was anterior cingulate cortex. The antisaccade practice group showed decreased activity across fMRI sessions; the prosaccade practice group showed no change in activity in this region. The role of anterior cingulate cortex in antisaccade generation is somewhat equivocal and in fact, it may play a number of different roles. One possibility is that is involved in signaling error likelihood (e.g. Johnston et al., 2007). As such, decreased antisaccade-related activity in this region over time for the group that practiced antisaccades might be due to the fact that after practice, participants were less likely to make errors or perceived that errors were less likely. Another possibility, given the putative role of ACC in response inhibition (e.g. Gaymard et al., 1998; Milea et al.,

2003) is that participants who practiced antisaccades were able to inhibit the response to look toward the peripheral cue more efficiently.

Summary

In the present study, behavioral and brain imaging data were collected before, during, and after practice of specific saccade tasks. The behavioral data provided information about how well the participants perform the tasks and whether they improve with practice. The data obtained from the fMRI sessions added information about the strength of activity at particular locations within the saccade circuitry, and the data from the EEG sessions provided information about the strength of activity at particular timepoints within the saccade trials. Thus, the multimodal nature of the present study has resulted in a more complete picture of how saccade practice affects behavior and brain activity.

The first thing to note is that activity in the majority of the regions in the saccade circuitry remained stable across time. This is an important replication of Raemaekers et al. (2007) because it underscores the fact that the basic saccade circuitry is stable. This was true for both the fMRI and EEG data. Second, the overwhelming majority of the changes observed were decreases in activity in saccade-related regions. The only exception was the increase in parietal cortex activity during the period preceding stimulus onset for prosaccades. This change corresponded to an increase in the number of express saccades made, which may be generated via a different mechanism than regular prosaccades. Also, this increase took place during a specific period of time, in preparation for the peripheral cue. The use of EEG in the present study allowed for the observation of changes confined to specific time periods, which are unlikely to be seen using fMRI alone.

It was expected that decreases in activity during pro- or anti-saccades would be specific to the participants who practiced that particular task. This was not always the case. In some regions, both groups showed a decrease in brain activity for a task, regardless of which task they practiced; however, it was never the case that the unpracticed group showed a decrease and the practiced group did not. The same was true for the behavioral measures. Only the prosaccade practice group decreased their prosaccade latencies and increased their percentage of express saccades, and only the antisaccade practice group showed any change in the percentage of correct antisaccades. Both groups, however, decreased their antisaccade latencies, although there was a trend toward a greater decrease in antisaccade latency for the antisaccade practice group. This suggests that the observed behavioral changes arise as a direct result of the practice.

Two brain regions, right DLPFC and IFG, showed the same pattern of change in antisaccade-related activity across fMRI sessions. Similar to the pattern of antisaccade latency, both groups showed decreased activity at the second fMRI session. In both regions, the antisaccade practice group showed a greater decrease than the prosaccade practice group, although not significant. The mere exposure to the antisaccade task at the first fMRI session may serve as practice for both groups. During the first session, participants learn to associate the stimuli with the correct response and gain practice in performing an antisaccade, a task they have not previously encountered. The results from the present study suggest that the greatest decrease in latency and brain activity in regions supporting cognitive control may occur after the very first session. Future studies may benefit from a short antisaccade practice session for all groups prior to the first fMRI session in order to observe changes in performance and brain activity related specifically to practice of the task, rather than simply experience with the task instructions.

Nevertheless, there were antisaccade-related regions that showed decreased activity specific to the antisaccade practice group. Activity in posterior brain regions involved in visual stimulus registration and saccade vector inversion decreased with practice. The change in visual cortex activity was limited to a specific period of time after stimulus presentation and was observed with EEG. Activity in visual cortex was significantly decreased at the third practice session, which corresponds to the session in which participants made the fewest direction errors.

In parietal cortex, decreased activity was observed in the fMRI data. Activity associated with vector inversion was confined to a specific location within parietal cortex, the precuneus. While vector inversion could be seen in the EEG data because the time resolution allowed for the observation of a shift in the source location from contralateral visual cortex to ipsilateral parietal cortex, it was in the fMRI data, which has high spatial resolution that the changes in precuneus activity across sessions were detected.

Conclusion

The behavioral and brain imaging techniques used in the current study complemented each other to yield information about how practicing saccade tasks can affect the performance of pro- and anti-saccades and the neural circuitry supporting these tasks. While the saccade circuitry was stable for the most part, subtle changes were observed, both in behavior and brain activity during and as a result of practice. Results from the present study suggest that changes in brain activity after practice of saccade tasks reflect both (1) decreased reliance on regions supporting cognitive control and (2) increased efficiency in the neural circuitry specific to saccade tasks.

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