Neural Basis of Inhibition: A Study of Antisaccades Using fMRI and MEG

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Abstract

Inhibition is a cognitive ability that allows humans to respond flexibly rather than reflexively to events. The purpose of this investigation is to elucidate the neural basis of inhibition in healthy humans. Combining magnetoencephalography and functional MRI, two unqiue brain imaging instruments, allows both key brain regions and the timing of neuronal processes involved with inhibition to be resolved. The study found strong evidence that the dorsolateral prefrontal cortex is an important component in programming inhibitory signals.

1 Introduction

1.1 The Antisaccade Task

The analysis of eye movements has long been used as an important diagnostic tool in neurology. Its use is usually neglected in the diagnosis of brain disorders and only recently has it become clearer that a variety of neurological disorders are associated with an inability to inhibit saccades[1]. The ability to suppress reflexive responses and to generate voluntary motor commands is crucial for everyday life because it frees the organism from a stimulus-driven behavior in favor of the achievement of internal goals. It is possible to examine this ability in one oculomotor task by presenting a visual stimulus at one side and asking the subject to look to the opposite side. A deficit in the inhibition of reflexive responses will result in a high number of saccades towards the visual stimulus, prosaccades (Figure 1a) and a low number of saccades to the opposite side, antisaccades (Figure 1b). This task was introduced by Peter Hallett in 1978 as a "novel task" and is now called the antisaccade task[12].

In the last 10 years, a large number of clinical studies have been conducted ranging from studies with patients with discrete lesions to those with psychiatric disorders. Functional imaging techniques have been applied to discover the brain areas involved in the generation of antisaccades. Basic research has characterized the properties of antisaccades and the conditions which lead to errors in this task. The findings obtained so far suggest that the antisaccade task can—with certain restrictions—be applied as a diagnostic tool for diseases affecting cortical and subcortical structures[8]. Deficient inhibition is characteristic of disorders such as schizophrenia, bipolar disorder, unipolar depression and obsessive compulsive disorder. Understanding the neural circuitry involved with the generation of antisaccades will contribute to a more complete understanding of inhibition deficits and lead to rational interventions.

[1] A saccade is a rapid eye movement that brings the point of gaze to the image of interest.

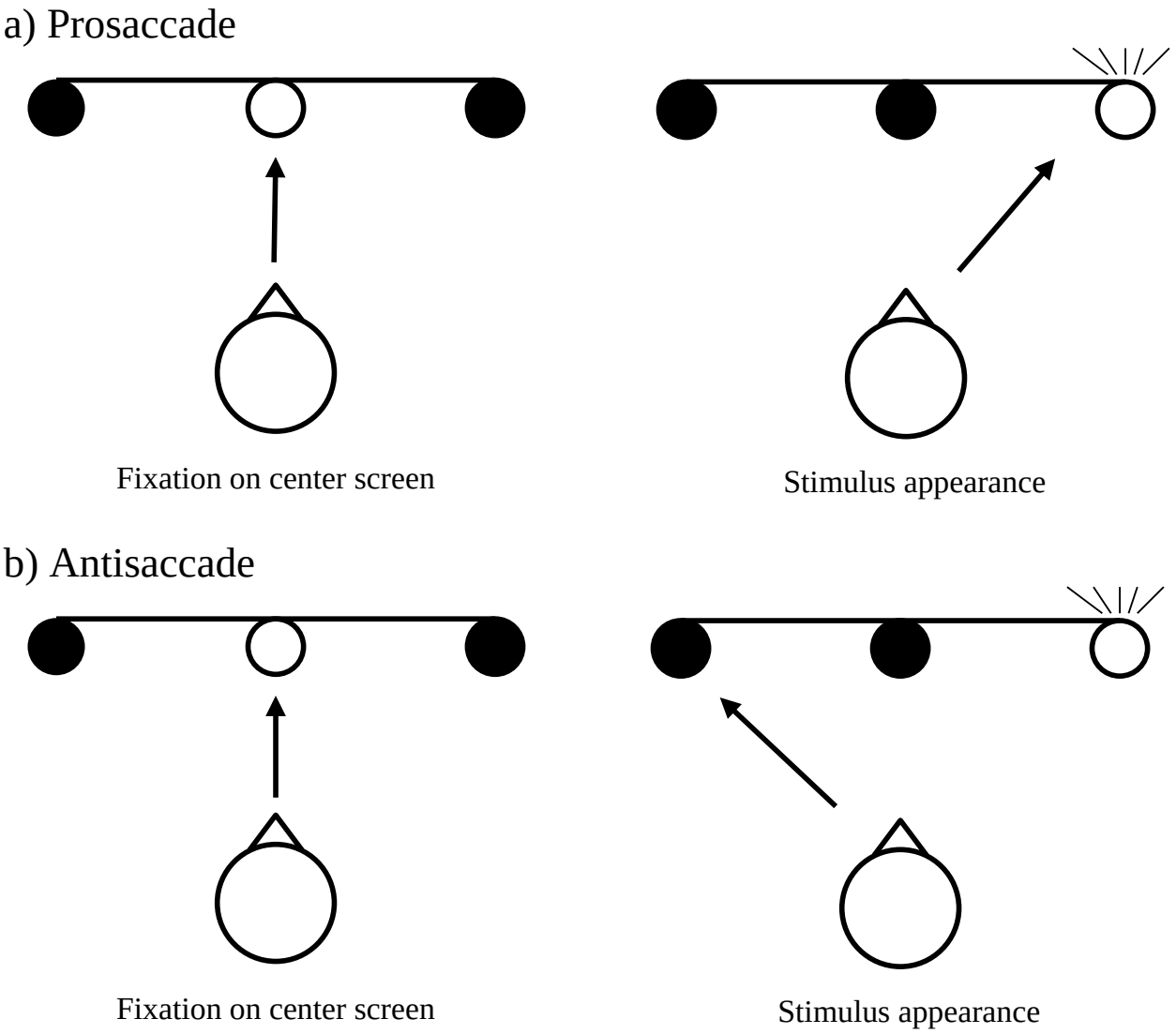


Figure 1: Two types of saccades. (a) Prosaccades are reflexive and directed *towards* the target. (b) Antisaccades are directed *away* from the target.

1.2 Studying the Neural Basis of Antisaccades

Previous studies of both human and non-human primates using an array of neuroimaging techniques have mapped out the processes involved in the generation of prosaccades (Figure 2). They converge in identifying the posterior parietal cortex (PPC) and frontal and supplementary eye fields (FEF, SEF) as being important components[1, 9, 18]. Use of temporal data has determined PPC activation to precede activation in frontal regions[19]. While the neural basis of normal saccades has been elucidated, understanding of antisaccades is less complete. This study aims to discover the key brain regions, neural circuits, and timing of neuronal processes that characterize antisaccades and inhibition.

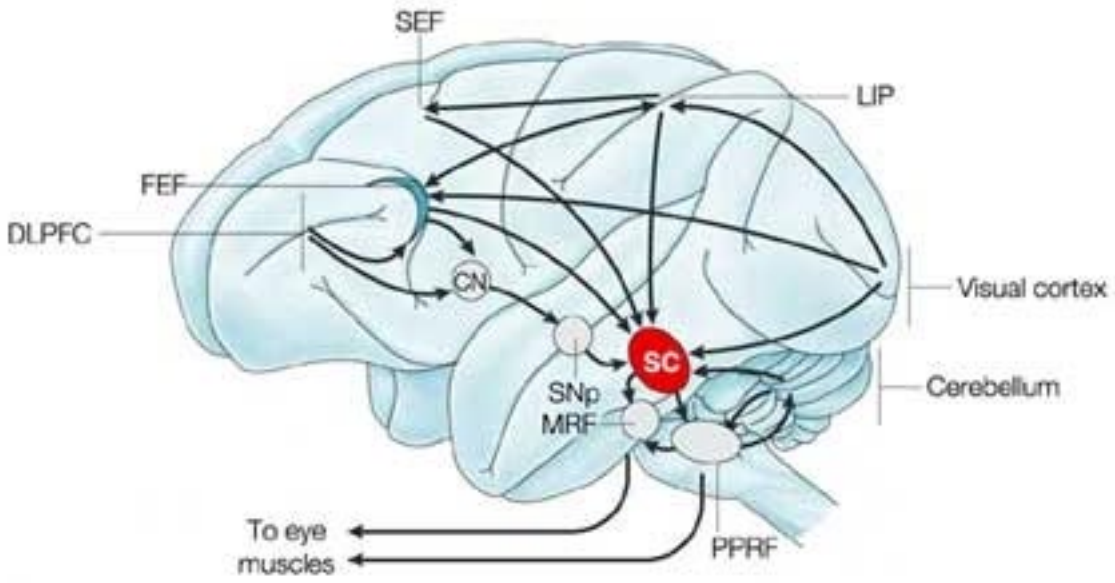


Figure 2: Structures believed to be involved in the generation of a saccade. A simplified schematic of neural activation is shown, with activity beginning in the visual cortex. CN, caudate nucleus; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; LIP, lateral intraparietal cortex; MRF, medullary reticular formation; PPRF, paramedian pontine reticular formation; SEF supplementary eye field; SC, superior colliculus; SNp substantia nigra pars reticulata. Image obtained from [10].

Unfortunately, isolating a single neurocognitive function for study has proven to be difficult in the past. Efforts are often confounded because the tasks employed to study such

functions involve more than one neurocognitive function[2]. In this study, saccadic inhibition is investigated using a setup from a recently completed project that isolates saccadic inhibition for study[13].

Subjects of this study were asked to perform a large number of both antisaccades and prosaccades. During performance of the task, neural activity will be recorded using functional MRI, which provides high spatial resolution, and magnetoencephalography (MEG) or electroencephalography (EEG), which provide high temporal resolution. The larger goal of using this data for antisaccade study is divided into three separate aims.

Aim 1 of this study is to determine whether antisaccades are associated with increased activation in the dorsolateral prefrontal cortex (DLPFC). Several studies examining regions of increased cerebral blood flow associated with the performance of antisaccades have yielded different results. McDowell *et al.* and Doricchi *et al.* demonstrated increased activation in the DLPFC as well as several other locations[15, 6]. However, Paus *et al.* found significantly greater activation only in the anterior cingulate cortex and the posterior parietal cortex during the performance of an antisaccade task compared to the activation during a prosaccade task[17]. In contrast, O'Driscoll *et al.* observed increased activation in the FEF, the supplementary motor area, the thalamus, the putamen, the superior parietal lobe and area 17 during antisaccades compared with prosaccades[16]. This study attempted to resolve this issue by comparing neural activation during antisaccades to activation during prosaccades by using fMRI data.

Aim 2 of this study focuses on finding the importance of DLPFC activation in the generation of correct antisaccades. If the DLPFC is a crucial component in inhibition, then error antisaccades should be associated with its failure, indicating that correct antisaccades can be generated only when that region is active. This aim was studied by comparing areas of activity, determined by fMRI, during performance of correct antisaccade trials to activity during error antisaccades. Because of the great number of saccadic trials each subject must

perform, error antisaccades are common. This study used an event-related fMRI method that allowed error and correct antisaccade trials to be studied separately and compared[5].

Aim 3 of this study is to determine when inhibition occurs relative to the onset of the saccade. Evidence is replete suggesting that the timing of neuronal processes across regions may be key to understanding neurocognitive functions[11]. Because the temporal resolution of fMRI is insufficient to study this aim, MEG data will be used. If the DLPFC is determined by fMRI to be activated or deactivated in error antisaccades, the change must occur before the onset of the actual saccade. MEG can find whether this is the case and also when exactly the signal is sent. A recent EEG study found evidence of frontal brain activity specific to correct antisaccade performance 160–60ms before onset of the saccade[3]. Other studies have found that frontal inhibition occurs in the last 100ms prior to the generation of a correct antisaccade[7].

2 Methods and Materials

2.1 Subjects

Twelve healthy right-handed subjects, seven females and five males, participated in the study after providing informed consent. Their ages ranged from from 19 to 39 (average age: 23.2 yr). Subjects were free of neurological or psychiatric illness and were screened to exclude substance abuse and depression in the past six months. Socio-demographic and neurocognitive information such as verbal IQ and socioeconomic status was collected from each subject. Subjects were compensated to participate in the study.

2.2 Visual Stimulus

The visual stimulus consisted initially of a white fixation ring of diameter 1.0° (measured in terms of degrees in the visual field) centered on a dark background (See figure 2). The fixation ring was flanked by two 0.7° white dots placed 10° right and left of center. At the start of a trial, the central fixation ring was replaced by one of two prompts. For half of the subjects, a yellow "O" 4.5° in diameter was the cue for a prosaccade, and a blue "X" spanning 4.5° was the cue for an antisaccade. For the other half, the "O" was the cue for an antisaccade and the "X" prompted a prosaccade. Prompts lasted 300ms before being replaced by the central fixation ring. The fixation ring disappeared after 1700ms, and a similar ring appeared around one of the two peripheral dots, the side randomly determined. This signaled the subject to make their saccade quickly and accurately. The white ring remained to the side for 1000ms during which time subjects can fixate the target. The white ring then returned to the center for 1000ms before the start of the next trial. One complete trial lasts 4000ms. Each run consisted of 26-46 of each trial type.

Antisaccade and prosaccade trials were randomly intermixed with the fixation baseline condition, which occurred about every 5th trial. The display during fixation was the same as the display during the cue to target interval. 10–17 fixation trials were present in each run.

2.3 Saccadic Measurements

The ISCAN® fMRI Remote Eye Tracking Labratory was used to record saccades during fMRI scanning. An ISCAN imaging video camera captured images of eye during performance of the saccadic tasks. The eye images were sent to ISCAN's RK-726PCI high resolution tracker located outside the fMRI room. The point where the eye was looking was determined by ISCAN's eye tracking and calibration processors.

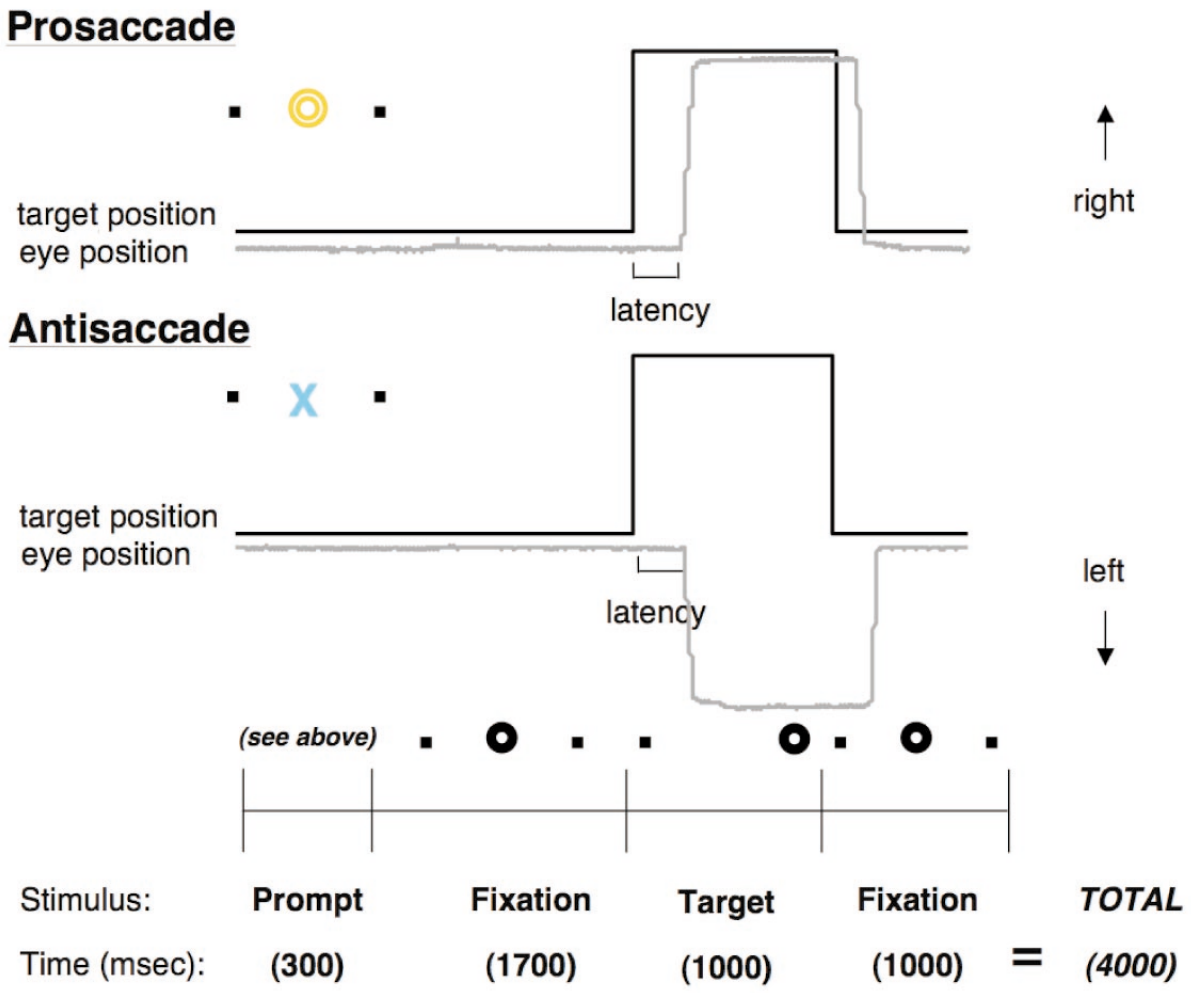


Figure 3: Trial illustration. Progress over time is from left to right. Top lines show horizontal position traces of targets (black smooth lines) and eyes (grey irregular lines) for a correct prosaccade (top) and antisaccade (below). Rightward motion is shown as up, by convention.

During MEG scanning, the direction of eye movement was recorded using Electrooculargram (EOG) sensors, placed above and below one eye and on the left and right of the head. EOG is very sensitive to the detection of saccadic onset.

The raw data obtained directly from ISCAN and EOG took the form of a series of waveforms indicating the direction of eye movement. The primary purpose of recording saccades is to identify correct and error trials. When a subject looked in the wrong direction indicated by the cue, the trial was scored as error, and the corresponding MEG or fMRI data for that trial was marked as brain activity associated with an incorrect response. Because data obtained from the instruments was often noisy, scoring was performed manually. In addition, MEG trials in which the subject blinked were discarded because blinks caused strong neural interference.

2.4 fMRI Procedures

The fMRI experiment consisted of a total of six runs of 5 minutes 22 seconds each. Each run had approximately 70 saccadic trials, split evenly between antisaccades and prosaccades. The six runs generated a total of 200 trials of each type per subject. The first two trials of each run was excluded from analysis. The total experiment time was approximately 40 minutes, including short rests between each run. The visual task was generated by a Macintosh computer using the Vision Shell libraries (MicroML, St. Hyachinthe, Quebec) and projected onto a mirror while the subject lay inside the fMRI instrument.

Structural images of the brain were first taken using anatomical MRI. Structural images are detailed anatomical pictures of a subject's brain but provide no information regarding activation. A 3 Tesla Allegra MR scanner (Siemens Medical System, Inselin, NJ) was used to take 2 high-resolution 3D rf-spoiled gradient echo T1 weighted scans. The procedure produced 128 1 x 1.35mm in-plane slices, each 1.3mm thick.

Anatomical data was used primarily to create 3D reconstructions of the brain on which

MEG and functional data could be mapped. The cortical surface was inflated to make activity buried within sulci more visible. The reconstructions were also morphed into a sphere for inter-subject registration, which matched together corresponding areas of activation for comparison across several subjects.

Functional MRI was used to determine which parts of the brain were activated by different stimuli. Functional scans were performed using the same 3 Tesla MR scanner. They were collected using Blood Oxygen Level Dependent (BOLD) contrast and a gradient echo T2 weighted sequence to measure variations in blood flow and oxygenation.

Functional scans were processed using the FreeSurfer Functional Analysis STream (FS-FAST) to produce statistical maps data for overlay on the structural data. Individual hemodynamic estimates were averaged together for the group using a fixed effects model, and statistical maps were created at every timepoint. Statistical contrasts were created for antisaccade versus prosaccade trials and antisaccade error versus antisaccade correct trials.

2.5 MEG procedures

The MEG task was identical to the fMRI experiment, except that eight runs were used instead of six to increase statistical power. Stimuli were generated by the same model Macintosh computer and projected onto a screen placed in front of the subject.

MEG data were acquired simultaneously in a magnetically and electrically shielded room. MEG signals were recorded from the entire head using a 306-channel SQUID Neuromag Vectorview. The signals were recorded continuously with 600 Hz sampling rate and were minimally filtered.

MEG data was analyzed using the MNE software package. The software was used to find minimum norm estimate (MNE) solutions to the MEG inverse problem. Solutions to the inverse problems are approximations of the areas of spatial activation in the brain. MNE solutions at each timepoint were overlaid on a 3D inflated brain to produce a movie of brain

activation.

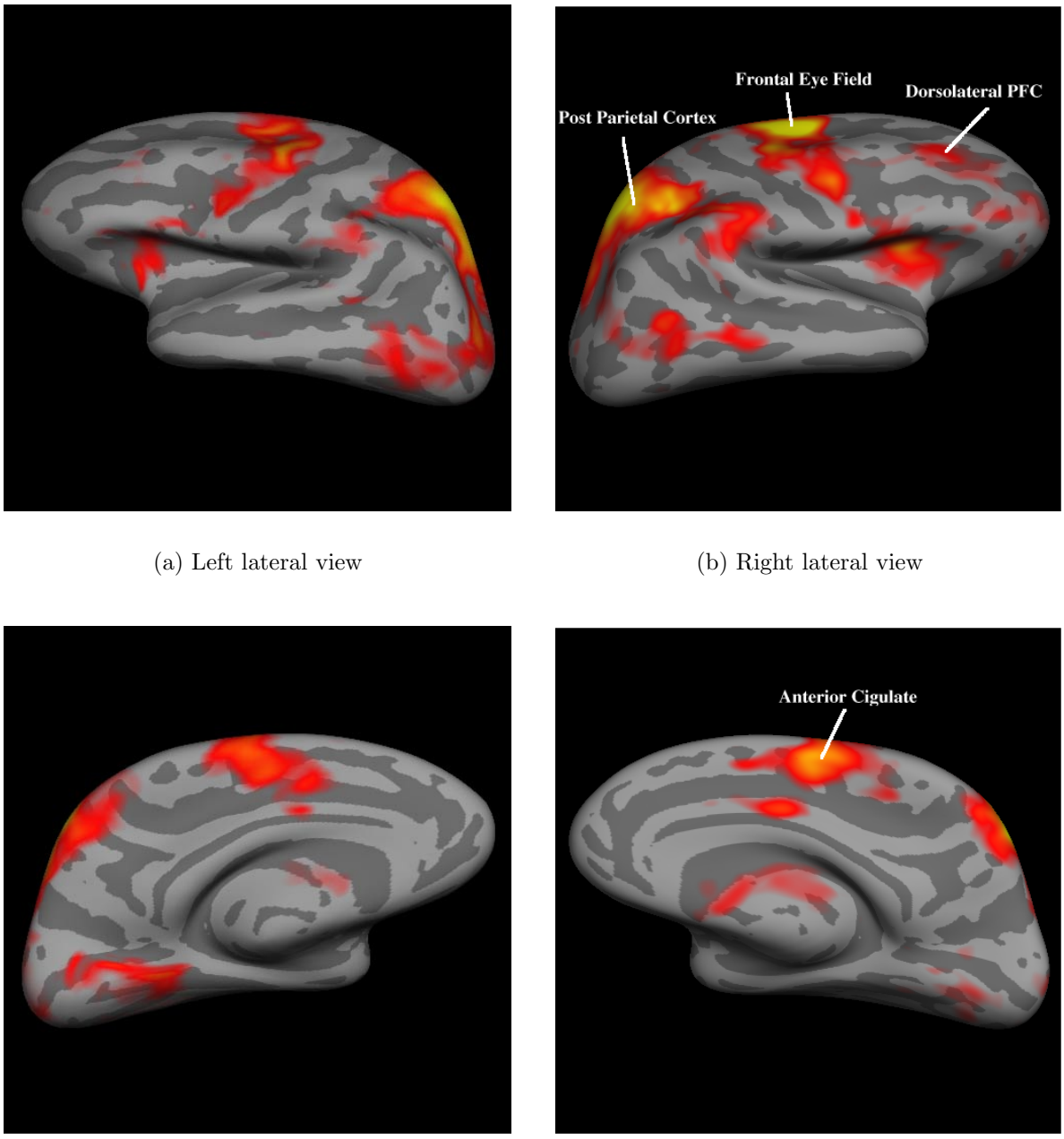
3 Analysis 1: Antisaccade vs Prosaccade

3.1 Results

Figures 4a–4d show the contrast in neural activation between antisaccades and prosaccades based on BOLD fMRI data. Spherical spatial normalization was used for this figure. The activation maps use functional data averaged across all 12 subjects using fixed effects analysis, making it more statistically powerful than analysis of any one individual. Voxels, or brain points, that are activated or deactivated to a statistically significant degree are mapped onto an inflated cortical model. Areas that show greater activation in antisaccades compared to prosaccades are red or yellow and areas of lesser activation are blue and white. The maps show activation averaged across all timepoints.

Examination of the lateral activation maps (Figures 4a and 4b) reveals increased activity in a distributed cortical and subcortical network of brain areas during antisaccades. The strongest activation occurs in the post-parietal cortex (PPC) and the frontal eye field (FEF). Activation in these regions are roughly symmetrical on the left and right hemispheres of the brain. Notably, the dorsolateral prefrontal cortex also exhibits increased activation in antisaccades with activity substantially stronger on the right hemisphere. The lateral maps show additional activation in the insular, occipital, and temporal regions. The medial view (Figures 4c–4d) displays activation in the anterior cingulate cortex on both hemispheres.

Figures 5a–5d show timecourse maps of neural activation in the lateral view, starting at 2 seconds after the prompt ("O" or "X") first appears. Images were taken every two seconds, but do not accurately reflect brain activation at that exact time due to the latency of hemodynamic response. The brain remains relatively stagnant until the map at 4 seconds, when activation is similar to that in Figure 4b: strong activation in the PPC and FEF and



(a) Left lateral view

(b) Right lateral view

(c) Left medial view

(d) Right medial view

Figure 4: Activation maps of Analysis 1: Antisaccade versus prosaccade. Lateral and medial surfaces on an inflated cortical model are displayed. Sulci are the darker stripes and gyri are the lighter stripes.

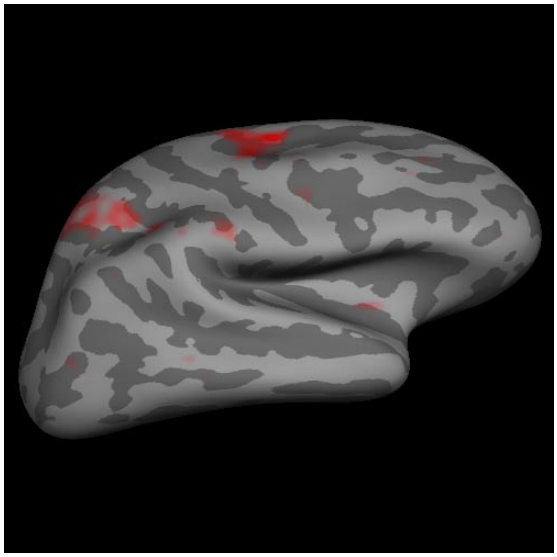
some activation in the DLPFC. Brain activity in those regions remains mostly intact at 6 seconds. Traces of activity in the FEF, PPC, DLPFC, and middle temporal gyrus remain at 8 seconds, though most brain activity had diminished.

3.2 Discussion

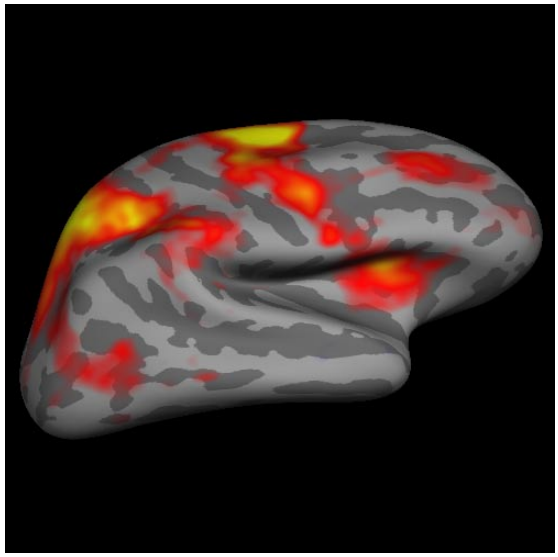
The activation shown in Figures 5a and 5b support the hypothesis that DLPFC activation is more present in antisaccades than in prosaccades. A natural extension to this conclusion is that dorsolateral activation plays a role in saccadic inhibition and perhaps inhibition in general. The results presented are consistent with findings by McDowell *et al.*[15] and Doricchi *et al.*[6] supporting the conjecture that prefrontal activation is involved in suppressing a reflexive response in favor a deliberate behavior. The fact that DLPFC activation is greater on the right hemisphere can be explained by a study showing that the right hemisphere is dominant for spatial attention, including saccades[14].

The results are consistent with literature indicating activation in areas outside the DLPFC. The FEF and PPC in particular are regions most commonly associated with saccadic inhibition and reported in other neuroimaging studies[17, 16, 18, 6]. Activation for these two regions was strongest in this study. The FEF, which controls premotor response to stimuli, the PPC, which integrates sensory information in cognition, and the DLPFC, traditionally ascribed to suppressing reflexive responses, all play logical roles in antisaccade generation. Other regions shown to be active such as the insula, temporal gyrus, and occiptal lobe have functions that do not appear to affect antisaccade generation and their activation was not consistently found in other studies.

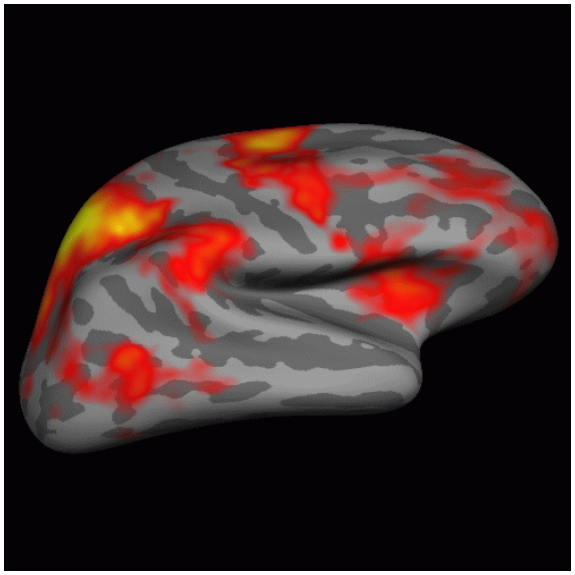
The timecourse images bring further support to the hypothesis that the prefrontal cortex plays a significant role in controlling antisaccades. Peak activation was shown in Figure 5b, 4 seconds after the initial prompt. The target (which the subject follows or looks away



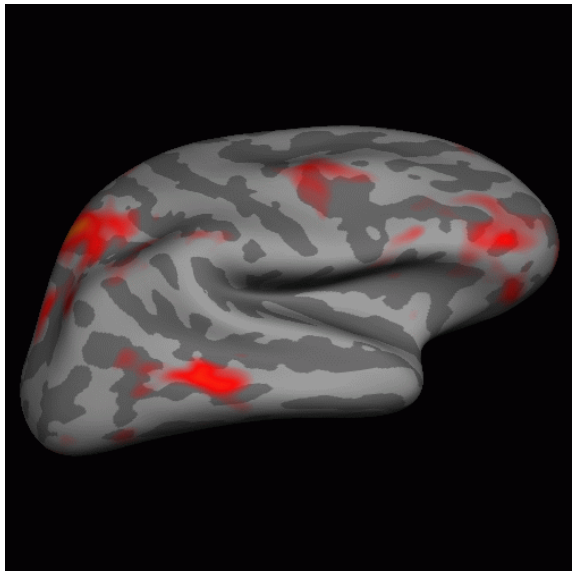
(a) Time = 2 seconds



(b) Time = 4 seconds



(c) Time = 6 seconds



(d) Time = 8 seconds

Figure 5: Timecourse maps of Analysis 1: Antisaccade versus prosaccade. Lateral surfaces on an inflated cortical model displayed from 2 seconds to 8 seconds after the prompt. Sulci are the darker stripes and gyri are the lighter stripes.

from) appears at 2 seconds, and considering an approximate 2 second hemodynamic lag[2], the activity shown in Figure 5 occurs around when the saccade is programmed. This gives strong support to the DLPFC being involved in antisaccade generation. If principal dorsolateral activation occured at 2 or 8 seconds, then it would not be possible that the DLPFC is involved in programming the inhibitory response because of timing. However, the temporal resolution of fMRI is quite poor and more complete data with regards to timing was collected from MEG (See Analysis 3).

However, whether each of these regions are absolutely crucial to inhibition cannot be determined by fMRI and MEG alone. These noninvasive studies can only bring support to associations between brain regions and their function in saccadic inhibition. The absolute importance of PPC, DLPFC, and FEF can only be determined by lesion studies, where those areas are completely impaired by lesions.

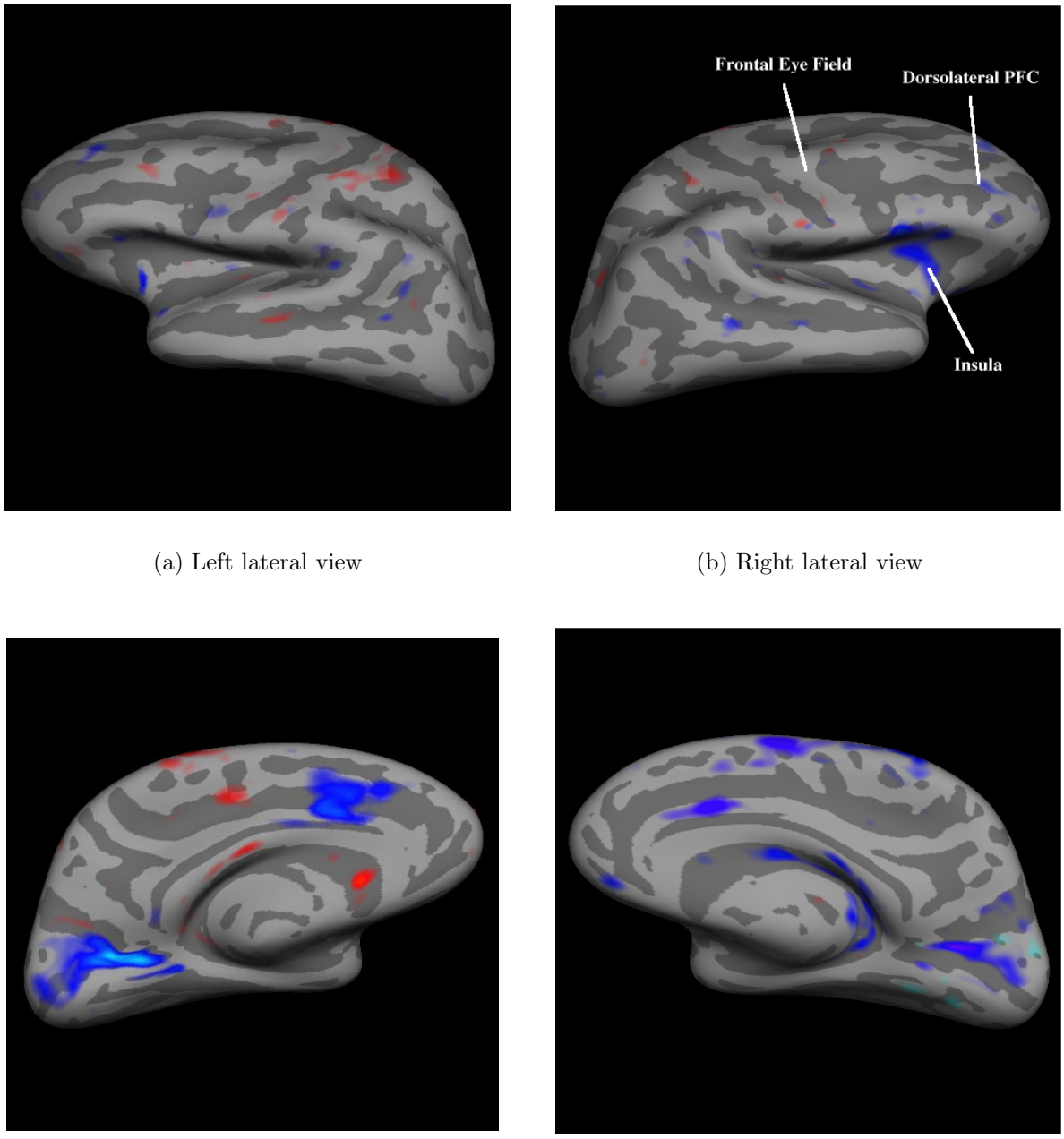
4 Analysis 2: Antisaccade error vs Antisaccade correct

4.1 Results

Figures 6a-6d are activation maps comparing brain activity associated with correct antisaccades and activity during error antisaccades. Areas of greater activation in correct trials are red and yellow and areas of deactivation are blue and white. The figures show activation across all timepoints. Like in Analysis 1, the contrast was mapped based on BOLD fMRI data and averaged across all 12 subjects using fixed effects analysis. Event-related fMRI was used to separate the functional data of correct and incorrect trials.

Table 1 shows the antisaccade error rate of each subject. While most error rates fall under 4%, a few individuals, notably 4 and 5, made significantly more errors. The cumulative error

[2]Hemodynamic lag is the time between which a neural response actually occurs to when it impacts bloodflow and is measured by fMRI.



(a) Left lateral view

(b) Right lateral view

(c) Left medial view

(d) Right medial view

Figure 6: Activation maps of Analysis 2: Antisaccade correct versus antisaccade error. Lateral and medial surfaces on an inflated cortical model are displayed. Sulci are the darker stripes and gyri are the lighter stripes.

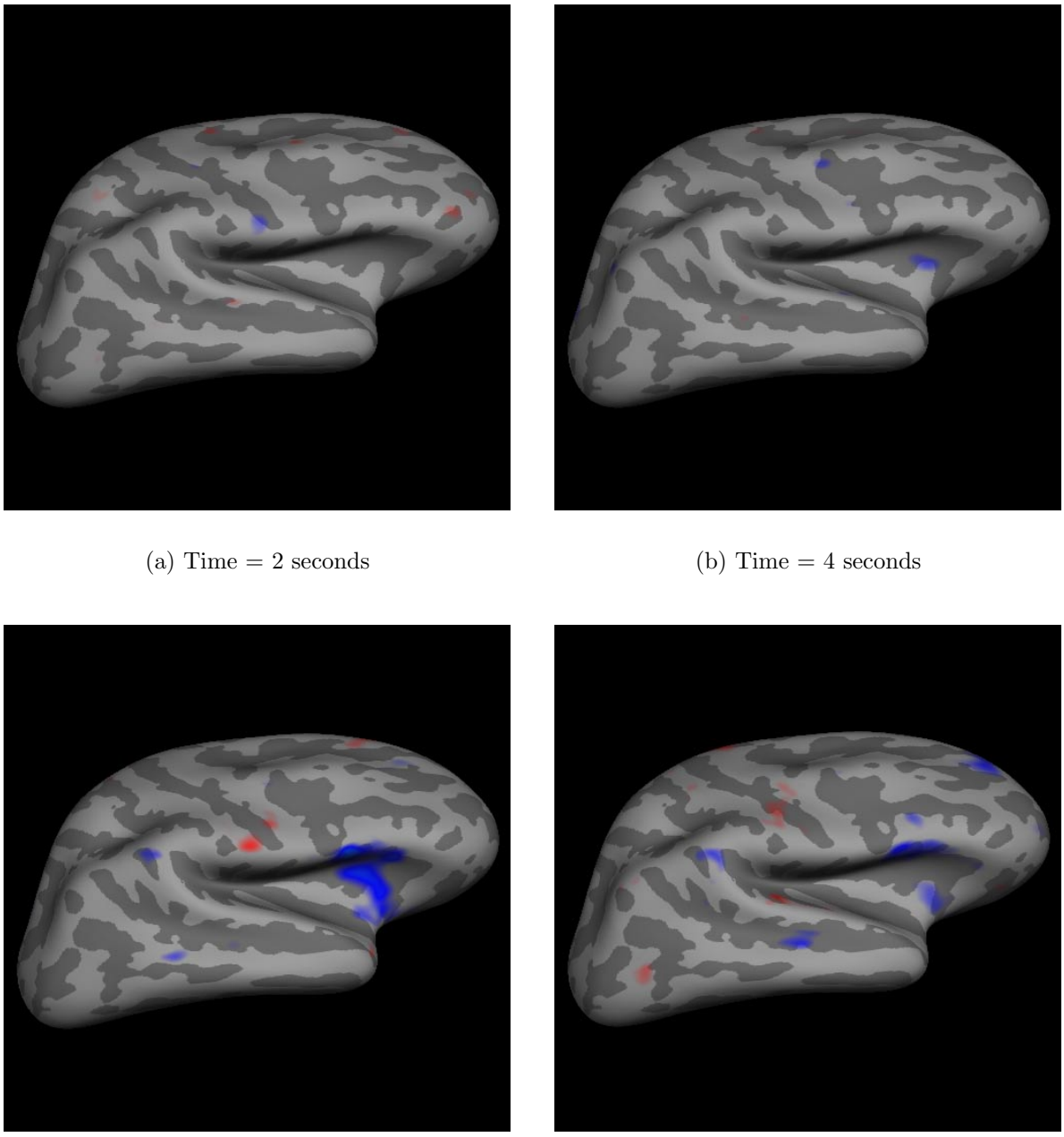
Subj. #	# Correct ASs	# Error ASs	Error rate
1	200	6	2.82%
2	209	4	1.88%
3	204	9	4.23%
4	180	33	15.49%
5	191	22	10.33%
6	210	3	1.41%
7	205	8	3.76%
8	202	11	5.16%
9	204	9	4.23%
10	196	17	7.98%
11	209	4	1.88%
12	209	4	1.88%
TOTAL	1320	130	5.09%

Table 1: Antisaccade error rates for 12 subjects.

rate is 5.09%, falling within the 5%–7% antisaccade error rate reported in [8]. The total number of correct antisaccades generated (1374) and error antisaccades generated (130) is great enough for statistically valid analyses.

Activation and deactivation are more subtle and more scattered than in Analysis 1. The lateral view (Figures 6a and 6b) shows deactivation in the DLPFC and FEF in both the left and right hemispheres. Deactivation is also present in the superior temporal gyrus on both hemispheres. Activation does occur along the frontal eye field in both hemispheres, especially on the left. The medial surface (Figures 6c and 6d) displays decreased activity in the anterior cingulate cortex in correct trials versus error trials, with stronger deactivation occurring on the right.

Figures 6a–6b are right lateral views of activation between 2 seconds and 8 seconds after the prompt is displayed. Scattered activity occurs between 2 seconds and 4 seconds in several regions of the brain. The strongest deactivation occurs at 6 seconds in the insula. Deactivation of DLPFC occurs at 6 seconds and 8 seconds after the prompt. FEF activation is present at 2 seconds and 6 seconds.



(a) Time = 2 seconds

(b) Time = 4 seconds

(c) Time = 6 seconds

(d) Time = 8 seconds

Figure 7: Timecourse maps of Analysis 2: Antisaccade correct versus antisaccade error. Lateral surfaces on an inflated cortical model displayed from 2 seconds to 8 seconds after the prompt. Sulci are the darker stripes and gyri are the lighter stripes.

4.2 Discussion

The results of Analysis 2 do not support the hypothesis that the DLPFC is associated with correct antisaccade generation. In fact, Figure 6 suggests the contrary—that DLPFC is more active in *error* rather than correct trials. However, the timecourse images (Figure 7) show that deactivation of the DLPFC occurred at 6 seconds and 8 seconds, much too late for the activity to have an impact in programming the antisaccade. At the same time, the data does not show activation of the DLPFC to occur when the inhibitory signal is sent. The poor temporal resolution of fMRI is not sufficient to resolve exactly when regional brian activity occurs; it only provides a rough estimate. The exact timing of neural process was studied using MEG (See Analysis 3).

Activation is displayed in the FEF, another region that studies have shown to be involved with antisaccades. The results presented do support conclusions made by O'Driscoll *et al.*[16] asserting that the FEF is the component that reflexive prosaccades in the antisaccade task. The timecourse data from this study does not actively support O'Driscoll's conclusions, as FEF activation occurs too early or too late to impact the inhibitory response. Again, additional temporal data was collected in Analysis 3.

Importantly, error antisaccades are more complex than correct antisaccade. While presumably only one pathway exists to generate a correct antisaccade, there are several reasons a subject may make an error. Factors that contribute to the failure in generating an inhibitory response may reasonably be associated with distinct neural processes.

Another confounding issue is the diversity of antisaccade errors. The simplest error occurs when the subject looks in the wrong direction. But often subjects look initially towards the wrong direction, realize their error, and then attempt to correct it by looking towards the correct direction; this response is known as a self-correct. In other instances, subjects do not respond at all to the stimuli and remain fixated on the center.

The most common type of error, the self-correcting error, are also the most complicated.

After the making the initial error, the subject must first realize the error and then attempt to correct it. All of these steps occur in a short timespan, so fMRI is unable separate these distinct processes. Conclusions drawn from this information may explain the increase in dorsolateral activation during error trials. In self-correcting errors, the subject still programs a correct antisaccade in the end, so presumably DLPFC activation would still occur. Activity due to other neural process that accompany the realization of the error may cause the increase in activity among error antisaccades. Realization is not a component to correct antisaccade generation.

Because error trials of each type (no response, no self-correction, and self-correcting) are not numerous enough, functional data for all types were averaged together for comparison with correct trials. Isolation of each error type and analyzing them separately may yield different results. But given the low rate of no response and non-selfcorrecting errors, the number of trials that need to be performed would be impractical.

5 Analysis 3: MEG Study of Temporal Activation

5.1 Results

Figure 8 shows frames from a movie of brian activation during antisaccade performance obtained from MEG data. The movies reflect the neural activation of a single individual. One image was obtained every 15ms between 1815ms–1950ms after the initial prompt ("O" or "X"). Target appearance occurred at 2000ms. The sources of activation determined from the raw MEG data were plotted onto an inflated surface. Areas of activation are marked as yellow.

The timeframe used for the images was locked to the onset of DLPFC activation. Activation was shown to begin at approximately 1800ms and lasted until 2035ms (Not shown).

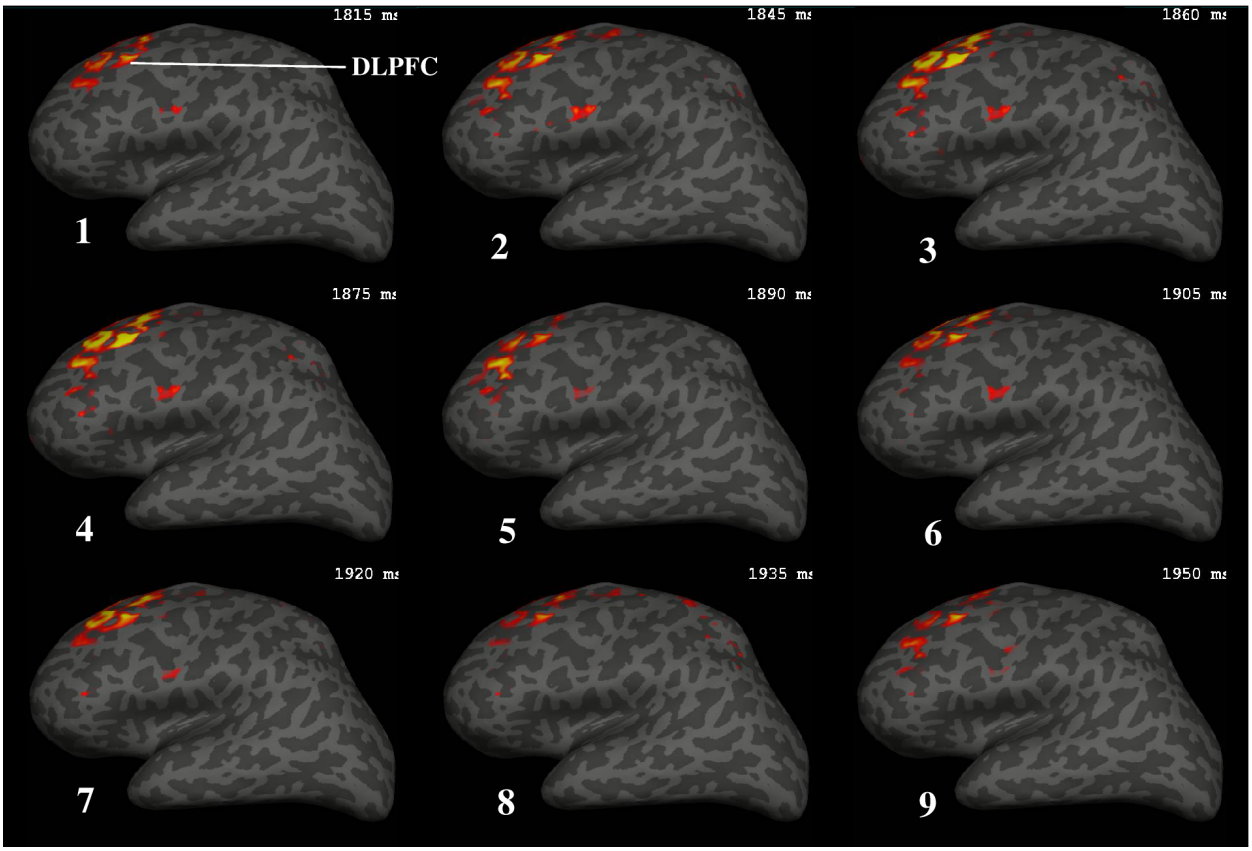


Figure 8: Frames from an MEG movie of activation in antisaccades from 1815ms to 1950ms. The left lateral hemisphere is shown. Sulci are the darker stripes and gyri are the lighter stripes.

5.2 Discussion

The information obtained regarding the timing of neural processes strengthened further the hypothesis that the DLPFC is important in programming an antisaccade. DLPFC activation was shown to occur approximately 200ms before appearance of the target until 2035ms, 35ms after the target appears. During this interval before the actual eye movement, the subject makes preparations to react to the target, programming an antisaccade or prosaccade depending on the cue given. The MEG data shows that dorsolateral activation occurs right during that programming timeframe. While not absolute confirmation that the DLPFC is important to inhibition, this is nonetheless strong support.

The 200ms pre-saccade timeframe for dorsolateral activity is similar to the study in [3], which found frontal activity specific to antisaccades 160-60ms before the actual saccadic movement. The 100ms of frontal inhibition prior to the antisaccade found in [7] is significantly less.

6 Conclusion

Strong evidence was found in this study supporting the hypothesis that the dorsolateral prefrontal cortex is an important component in saccadic inhibition. Both fMRI and MEG were used to provide high spatial and high temporal detail regarding the processes behind inhibition. Results from the fMRI phase of study show that the DLPFC is indeed more active during antisaccades than in prosaccades. Temporal data from MEG found that DLPFC activation occurs at the same time as when the inhibitory signal is sent. This suggests that dorsolateral activation is associated with the inhibitory response.

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