THE NEURAL SUBSTRATES OF DELAYED MATCH AND NON-MATCH SACCADES; AN FMRI INVESTIGATION

by

BENJAMIN PIYA AUSTIN

(Under the Direction of Jennifer E. McDowell)

ABSTRACT

The current fMRI study investigated the neural substrates of saccadic inhibition in humans using a delayed-match-to-sample (DMS) / delayed-non-match-to-sample (DNMS) paradigm adapted from Hasegawa et al.'s (2004) study of single-cell activity in monkeys. Fourteen normal subjects performed alternating blocks of DMS/DNMS tasks while fMRI data was acquired and eye-movements were recorded. Imaging results revealed increased activation associated with DMS in two areas of prefrontal cortex (BA 8 and BA 10) which may have contributed to prospective memory and working memory of a planned motor act, respectively. DNMS activation was observed in the circuitry known to support saccade generation including the right medial frontal eye field (FEF), supplementary eye fields, and posterior parietal cortex. The DNMS-related activity observed in the FEF may be the human analogue of the "don't look" signal described in the pre-FEF and FEF by Hasegawa et al. (2004).

Index words: delayed-match-to-sample, non-match-to-sample, fMRI, saccades, inhibition, FEF

THE NEURAL SUBSTRATES OF DELAYED MATCH AND NON-MATCH SACCADES; AN FMRI INVESTIGATION

by

BENJAMIN PIYA AUSTIN

B.E., Vanderbilt University, Nashville, 2003

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GEORGIA

2007

THE NEURAL SUBSTRATES OF DELAYED MATCH AND NON-MATCH SACCADES; AN FMRI INVESTIGATION

by

BENJAMIN PIYA AUSTIN

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

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
December 2007

ACKNOWLEDGEMENTS

I would first like to thank my advisor and mentor, Dr. Jennifer McDowell, for her support and guidance through the past two years. I would also like to thank the other members of my committee, Dr. Brett Clementz and Dr. Nash Unsworth. I also want to thank Dr. Kara Dyckman and Dr. Jazmin Camchong for teaching me AFNI. Finally, I would like to express my gratitude to Natalie Pichetti and Peter Elmasry for their assistance with behavioral data analysis. This research was supported by NIMH.

TABLE OF CONTENTS

Page

ACKNOWLEDGEMENTS iv

LIST OF FIGURES vi

LIST OF TABLES vii

CHAPTER

1 INTRODUCTION 1

2 METHODS 7

Participants 7

Procedure 7

Stimuli 9

Analysis 10

3 RESULTS 13

Eye Movement Data 13

FMRI Data 14

4 DISCUSSION 25

Behavioral Measures 25

FMRI Sessions 26

Conclusions 38

REFERENCES 39

LIST OF FIGURES

Page

Figure 2.1: Stimuli Presented During DMS/DNMS Task....12

Figure 3.1: BOLD Activity Associated with DMS/DNMS Task....16

Figure 3.2: BOLD Activity Associated with DNMS....19

Figure 3.3: BOLD Activity Associated with DMS....21

Figure 3.4: Percent Signal Change of ROIs Associated with DNMS....23

Figure 3.5: Percent Signal Change of ROIs Associated with DMS....24

LIST OF TABLES

Page

Table 3.1: Talairach Coordinates of the Centers of Mass for ROIs.....18

CHAPTER 1

INTRODUCTION

The inability to inhibit behaviors can compromise social norms and even survival. In monkeys, the inability to avoid eye contact with a dominant male monkey can be seen as an act of aggression (Mendelson et al., 1982; Van Hooff, 1972). In humans, the ability to suppress inappropriate behavior is equally as important to social interaction. For example, in conversation, one may be inclined to speak at an inappropriate time. Failing to inhibit an unwanted verbal response, e.g. interrupting another speaker, can be interpreted as an act of rudeness or disrespect.

The suppression of unwanted or inappropriate behaviors has been studied in both non-human and human primates, and brain circuitries often involving the prefrontal cortex (PFC) have been implicated in supporting inhibition (Hasegawa et al., 2004). Much of what is known about the neural substrates of inhibition comes from lesion (Iversen and Mishkin, 1970; Pierrot-Deseilligny et al., 1991; Rivaud et al., 1994; Gaymard et al., 1999), single-electrode (Iwabuchi and Kubota, 1998; Li and Kubota, 1998; Sakagami and Niki, 1994a, 1994b; Sakagami et al., 2001; Watanabe, 1986; Sommer and Wurtz, 2001), and neuroimaging (Camchong et al., 2006; Ford et al., 2004; Kawashima et al., 1996b; Kiefer et al., 1998; Konishi et al., 1999; McDowell et al., 2002; Milea et al., 2005; Perlstein et al., 2003; Sawaguchi, 1996) studies using simple motor tasks which can be manipulated to have an inhibitory component. Among these, ocular tasks provide a solid foundation for investigating the neural substrates of inhibition because the neural circuitry underlying saccadic eye movements is relatively well understood (Pierrot-Deseilligny et

al., 2003a; Schall et al., 2002b) and can be easily manipulated. In this way, changes in brain activations in neuroimaging studies can be associated with alterations of experimental design (Dyckman et al., 2007).

The basic suppression of saccadic eye movements requires two mechanisms - a fixation signal and a movement cancellation signal (Hasegawa et al., 2004). Fixation neurons have been identified in substantia nigra (Hikosaka and Wurtz, 1983), pons (Gandhi and Keller, 1999), and superior colliculus (Munoz and Wurtz, 1993) as well as frontal cortical regions such as the frontal eye field (FEF) (Bizzi, 1967; Segraves and Goldberg, 1987). These neurons, when engaged in active fixation, may inhibit the generation of saccades (Hasegawa et al., 2004). Studies in monkeys show that these neurons discharge tonically except in the interval around a saccade and that increased thresholds of electrical stimulation are required to evoke saccades from FEF (Goldberg et al., 1986) and superior colliculus (Schiller and Sandell, 1983) when a monkey is actively fixating.

Another mechanism that suppresses saccadic eye movements is a cancellation signal. Studies using a go/no-go (GNG) task, in which a visual cue instructs a subject either to reach or look to a target (“go”) or to withhold a response (“no-go”), suggest that this cancellation signal may be closely associated with prefrontal cortex. In monkeys, lesion studies suggest that damage to the dorsolateral prefrontal cortex (DLPFC) impairs GNG task performance (Iversen and Mishkin, 1970) and single-electrode studies report that neurons in this area respond selectively to the instructional cue (go or no-go) during the manual version (Iwabuchi and Kubota, 1998; Li and Kubota, 1998; Sakagami and Niki, 1994a, 1994b; Sakagami et al., 2001; Watanabe, 1986) as well as the oculomotor version (Sommer and Wurtz, 2001). In humans, imaging studies also report activation of the PFC during the GNG task (Casey et al., 1997;

Kawashima et al., 1996a; Konishi et al., 1998; Tsujimoto et al., 1997). Hasegawa et al. (2004) suggest that the fixation signal and the cancellation signal associated with the GNG task may be part of a global suppression mechanism, i.e., the suppression of all movements rather than the active suppression of a specific movement.

Other eye-movement tasks requiring saccadic inhibition also implicate frontal cortex circuitry in supporting task performance. The antisaccade task requires the inhibition of a glance to a newly appearing cue and the rapid redirection of gaze to the mirror image of that cue (Hallett, 1978). Unlike a pro-saccade, where the eye movement is visually-guided ("Look to the cue"), the anti-saccade is an intentional eye-movement and the target is signaled by the location of the peripheral cue through stimulus–response association (Hasegawa et al., 2004); the target is same in magnitude and opposite in direction.

The cortical circuitry supporting antisaccades is similar to that supporting prosaccades, with increased activation in regions supporting inhibition. For instance, more activity has been observed subcortically in striatum (Raemaekers et al., 2002, 2006a,b) and cortically in several regions including PFC (e.g. DeSouza et al., 2003; Matsuda et al., 2004; McDowell et al., 2002; Muri et al., 1998; Sweeney et al., 1996), FEF, supplementary eye field (SEF), and posterior parietal cortex (PPC) (e.g. Raemaekers et al., 2006a,b; Ford et al., 2005; Curtis and D'Esposito, 2003; Luna et al., 2001; Doricchi et al., 1997; DeSouza et al., 2003). In the antisaccade paradigm, the frontal lobe is thought to control inhibition of visually-guided saccades (Guitton et al., 1985) and may depend more specifically on DLPFC, as supported by lesion (Pierrot-Deseilligny et al., 1991), PET (Doricchi et al., 1997), and functional MRI studies (Sweeney et al., 1996; Muri et al., 1998). Other studies, however, report no such increased activation in PFC (e.g. O'Driscoll et al., 1995; Paus et al., 1993; Kimmig et al., 2001; Raemaekers et al., 2002,

2006a,b). When inhibition is effective, the triggering of correct intentional saccades may rely on FEF since isolated lesions of this region increase the latency of correct antisaccades (Rivaud et al., 1994; Gaymard et al., 1999). When inhibition is ineffective, errors in the antisaccade task, or unwanted visually guided saccades, are triggered mainly by the parietal eye field (PEF) within the PPC (Pierrot-Deseilligny et al., 2003a).

Pierrot-Deseilligny et al. (2003a) suggest that DLPFC may be the neural basis for working memory in temporal and spatial domains. PFC plays a role in the temporal domain of saccadic inhibition, specifically in the control of timing of predictive saccades (Pierrot-Deseilligny et al., 2003a). When both the location of the target and the timing of its occurrence are predictable, subjects, after only a few trials, normally begin to perform anticipatory, or predictive, saccades to the target before they are cued to do so (Pierrot-Deseilligny et al., 2005). In humans, lesions to the FEF and DLPFC lead to decreased percentage of anticipatory saccades (contralateral and bilateral, respectively) (Pierrot-Deseilligny et al., 2005; Rivaud et al., 1994). DLPFC is also involved in the maintenance of spatial information (Leung et al., 2002). Spatial working memory is often studied using the memory-guided saccade (MGS) paradigm. The MGS task requires the subject to remember the location of a target flashed in the peripheral visual field while fixating a central point, and then, after a delay of several seconds or more, to make a memory-guided saccade to the remembered position of the flash (Pierrot-Deseilligny et al., 2005). Studies in humans show that DLPFC controls short-term spatial memory, probably up to delays of 15-20 seconds, after which the medial temporal region could take over the control of medium- and long-term spatial memory (Ploner et al., 1998, 2000).

As tasks requiring saccadic inhibition often require simultaneous spatial attentional processes (e.g., antisaccade and memory-guided saccade tasks), the investigation of the neural

substrates supporting inhibition are confounded by those supporting visual-spatial attention. A recent study by Hasegawa et al. (2004) solves this confound by using a paradigm that maintains spatial attentional demands across tasks while varying inhibitory components. Using a delayed-match-to-sample (DMS) / delayed-non-match-to-sample (DNMS) task, Hasegawa et al. (2004) measured electrical activity of 310 single neurons in the FEF and pre-FEF of two rhesus monkeys and reported that these prefrontal neurons are involved in coding the suppression of specific saccades. The tasks required the monkeys to fixate on a central target while a peripheral cue was briefly presented and to maintain the spatial location of that cue over a delay period (2.5 sec). Upon extinction of the fixation target, the monkeys generated a saccade to one of two peripheral targets: one at the location of the previously presented cue (DMS), or the other at an unpredictable location (DNMS). As such, during DNMS, the monkeys had to inhibit a response to the cue while preparing a response to a yet to be identified target. The results described “look” and “don’t look” prefrontal neurons that carried signals selective for the targeted or forbidden stimulus, respectively. The activity of these neurons correlated with the monkeys’ success or failure on the task and suggest that the parallel representation of look and don’t look prefrontal neurons must be important for the brain to plan appropriate movements while simultaneously inhibiting inappropriate movement (Hasegawa et al., 2004).

The Hasegawa DMS/DNMS task implicates FEF and pre-FEF neurons in the mediation of intended and unwanted behaviors in monkeys, but until now, the paradigm has not yet been conducted in humans. In the current study, functional magnetic resonance imaging (fMRI) and eye movement data were collected while fourteen human participants completed two runs of the Hasegawa DMS/DNMS task.

While both DMS and DNMS require the initial inhibition of gaze to the sample cue, DNMS requires a “don’t look” signal to be sustained over the delay period. We hypothesize that this “don’t look” signal will increase activation in cortical areas known to support inhibitory tasks, such as the antisaccade task. These regions may include FEF, SEF, and precuneus (e.g. Raemaekers et al., 2006a,b; Ford et al., 2005; Curtis & D’Esposito 2003; Luna et al., 2001; Doricchi et al., 1997; DeSouza et al., 2003) as well as regions in PFC (e.g. DeSouza et al., 2003; Matsuda et al., 2004; McDowell et al., 2002; Muri et al., 1998; Sweeney et al., 1996). Also, the original study in monkeys showed no significant behavioral differences between DMS and DNMS for either latency or percentage of correct trials. Thus, we hypothesize similar behavioral results for humans in the current study, i.e., DMS will not significantly differ from DNMS in either latency or rate of error.

The purpose of the current study is to determine if there is a human analog of the “look” and “don’t look” signals found in FEF and pre-FEF in monkeys. Fourteen subjects will perform two runs of the Hasegawa DMS/DNMS paradigm while fMRI and eye movement data are collected.

CHAPTER 2

METHODS

Participants

Fourteen normal participants (mean age = 26.4 years, SD = 2.3; 100% right-handed, 7 female participants) were studied. Participants were recruited from a pool of graduate students from the University of Georgia. All participants were free of serious physical health problems and absent of known neurological hard signs. Exclusion criteria included loss of consciousness or a history of severe head trauma or drug abuse. Participants were also screened for contraindications for fMR imaging (e.g., metal in their bodies). All participants were recruited from UGA student body and provided informed consent as per University of Georgia Institutional Review Board approval.

Procedure

FMRI Session

Brain imaging was performed at the Athens Orthopedic Clinic MRI Center using a GE Signa Horizon LX 1.5T MRI scanner (Milwaukee, Wisconsin). During imaging, the head was stabilized with a cushioned positioning system and forehead restraints. Earplugs reduced scanner noise by approximately 30 dB. Stimulus presentation was controlled using Presentation software (Neurobehavioral Systems, Albany, California). An LCD Projector (NEC Viewtechnology, Ltd., Tokyo, Japan) cast stimuli onto a rear projection screen that stood approximately 174 cm from the participant's nasion. A dual mirror box designed specifically to

make: 1) stimuli visible to the participant and 2) the participant's eyes visible to an eye tracking camera, was placed 16 cm above and in front of the participant's eyes.

MRI Eye Tracking

Eye movements were recorded using MRI compatible equipment (MEyeTrack LR, SensoMotoric Instruments, Inc., Berlin, Germany). The eye was illuminated via an infrared light source placed above the eye and the image was relayed via a remote infrared camera with long-range optics. Prior to the first task, a calibration trial was run. Based on the calibration, the X and Y coordinates at the center of the participant's pupil were recorded for each sample point. The pupil coordinates were recorded in reference to the corneal reflection. After calibration, eye movements were displayed on a computer monitor so performance could be monitored continuously by the experimenter and data were recorded (sampling rate = 60 Hz) for later analysis.

Scanning Parameters

Immediately prior to entering the scanner, participants viewed the practice stimuli and reviewed task instructions. After positioning participants in the scanner, a three-dimensional T1-weighted structural magnetic resonance imaging (MRI) scan with high resolution was collected (spoiled gradient recall (SPGR) protocol, matrix 256 × 256, 24 cm field of view (resulting in an in-plane resolution of .97 × .97), slice thickness of 1 mm, echo time [TE] 2.8 milliseconds, repetition time [TR] 10.8 milliseconds, flip angle 20º, sagittal acquisition, 124 slices, scan time 5 minutes 41 seconds) for definition of anatomical structures within each brain. Following the structural scan, T2*-weighted functional images were obtained with an axial prescription, using a spoiled gradient pulse sequence with a spiral readout pattern in k-space (matrix 64 × 64, 24 cm field of view (resulting in an in-plane resolution of 3.75 × 3.75), slice thickness of 4 mm, TE 40

milliseconds, TR 1.9 seconds with two interleaves, for an image acquisition time of 3.8 seconds; flip angle 77º, 24 slices, scan time 6 minutes 54 seconds) (Glover and Lai, 1998). The volume of brain coverage for functional scans was defined by placing the most superior scan plane tangent to the highest point of the somatosensory cortex.

Stimuli

Each participant performed 2 runs of the modified Hasegawa DMS/DNMS task (Run #1 and Run #2). The block design runs were identical except that trials within blocks were pseudorandomized. Each run consisted of 30.0-second blocks of DMS trials (n = 6 blocks; six trials in each block) alternating with 30.0-second blocks of DNMS trials (n = 5 blocks; six trials in each block). Each trial consisted of four distinct periods: fixation (1000 milliseconds), sample (500 milliseconds), delay (2500 milliseconds), and test (1000 milliseconds). For each trial, the fixation period consisted of a cross presented in the middle of the screen. During the sample period, the fixation cross remained and a 1^{o} white dot was presented at one of six pseudorandomly selected peripheral locations (8^{o} right, 8^{o} left, 4^{o} right and 4^{o} up, 4^{o} left and 4^{o} up, 4^{o} left and 4^{o} down, or 4^{o} right and 4^{o} down). During the delay period, the peripheral cue was removed and only the fixation cross remained. During the test period, the fixation cross disappeared and the subject was presented with two cues – one cue at the same peripheral position as the dot presented during the sample period and the other cue at one of the five remaining peripheral positions. The participants were instructed to fixate on the cross as long as it was present, even while the peripheral cue was introduced. Then, upon extinction of the fixation target and presentation of the two peripheral cues, participants were to move their eyes as quickly as possible to the previously introduced peripheral cue (DMS) or the cue at the new location (DNMS). DNMS trials were distinguished from DMS trials by the identity of the

fixation cross; DNMS was denoted by a fixation cross surrounded by a diamond, and DMS was denoted by a fixation cross surrounded by a box. Each trial lasted for 5000 milliseconds, and each run lasted for approximately 5 minutes and 30 seconds (see Figure 2.1).

Analysis

Behavioral Analyses

Eye movements recorded during the fMRI scanning sessions were analyzed using programs written in Excel (Microsoft, Redmond, Washington) for 1) the percentage of trials with correct responses and incorrect responses (an initial saccade generated to the incorrect target during the test period) and 2) the latency of memory saccades (time in milliseconds between fixation offset and the start of the saccade [>90 milliseconds] (Fischer et al., 1993; Wenban-Smith and Findlay 1991)).

FMRI Analyses

Analyses were conducted using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). Three-dimensional datasets were created from individual image files. For each participant, all volumes were registered to the middle volume to correct for minor head movement over time. To control for differences in baseline intensity across participants, functional data were normalized to the mean of each voxel across the run. A full width, half-maximum (FWHM) Gaussian filter of 4 mm was applied to the data to account for individual variations in anatomy. Deconvolution analyses were used to examine percent signal changes between the baseline (DMS) and experimental (DNMS) tasks across time. The two separate runs were then concatenated to increase signal to noise ratio. To evaluate task-related blood oxygenation level-dependent (BOLD) signal change (i.e., “activation”), six factors were entered into a regression model including the experimental and baseline conditions, one linear drift

factor, and three motion parameters (i.e., roll, pitch, and yaw). Anatomical and functional volumes were transformed into Talairach space (Talairach and Tournoux, 1988) and resampled to 4 × 4 × 4 mm resolution.

To display task-related BOLD signal change, data were submitted to *t* tests on a voxel-by-voxel basis. Results from within-group one-sample *t* tests show areas with significant signal change between the DMS and the DNMS conditions. To protect against false positives, a threshold/cluster method derived from Monte Carlo simulations (accounting for the 4 mm FWHM Gaussian filter and with a connectivity radius of 5.7 mm) was applied to *t* maps (Ward, 2000). Based on these simulations, the familywise alpha of .05 was preserved with an *a priori* voxelwise probability of .025 and three-dimensional clusters with a minimum volume of 704 μL (11 or more voxels). The resulting averaged, clustered *t* maps were used to identify regional BOLD signal changes associated with DNMS performance within each group (compared to DMS performance).

The nature of the relationship in the brain regions with significant activity was examined via a region of interest (ROI) analysis. ROIs were determined based on BOLD activations observed in the present data. For each ROI, a sphere (radius 8mm) was positioned at the center of mass of each region that showed a significant effect. Mean percent signal change for each run was calculated for each ROI for each individual and group averages were obtained.

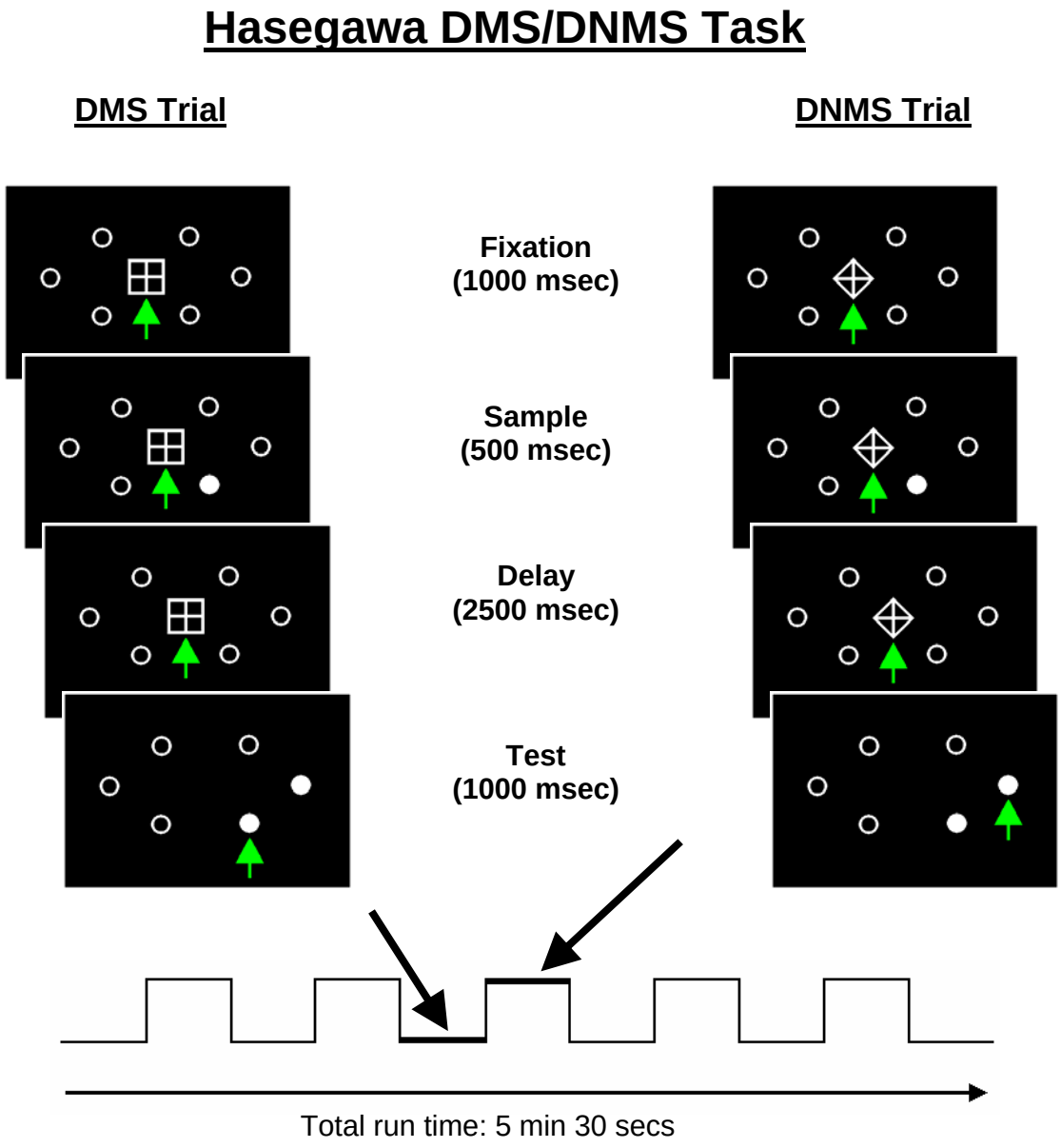

Figure 2.1 Stimuli Presented During DMS/DNMS Task
Participants performed 30-second blocks of DMS with 30-second blocks of DNMS. Green arrows show correct eye position. DMS, delayed-match-to-sample; DNMS, delayed-non-match-to-sample.

CHAPTER 3

RESULTS

Eye Movement Data

Scorable behavioral data were available for 50% of participants during the first task run and 65% of participants during the second task run. Data from one subject was dropped from analysis for failure to complete the task. For all other cases, failure to score a participant's data was due to technical problems.

Analyses revealed no significant differences between DMS Run #1 (N=6) and DMS Run #2 (N=8) in either percentage of correct trials (M_1 = 90.9%, SD_1 = 12.2; M_2 = 89.2%, SD_2 = 15.5) or average saccade latency (M_1 = 238ms, SD_1 = 42.0; M_2 = 246ms, SD_2 = 54.9). Similarly, analyses revealed no significant differences between DNMS Run #1 (N=6) and DNMS Run #2 (N=8) in either percentage of correct trials (M_1 = 91.3%, SD_1 = 8.9; M_2 = 93.3%, SD_2 = 9.9) or average saccade latency (M_1 = 301ms, SD_1 = 57.0; M_2 = 320ms, SD_2 = 62.6). Thus, task-specific behavioral performance was statistically consistent across runs.

When the two runs were collapsed, analyses were conducted comparing performance of DMS (N=14) with DNMS (N=14). Results showed that the percentage of correct trials for DMS (M = 90.0%, SD = 13.7) did not differ significantly from DNMS (M = 92.5%, SD = 9.2). Average reaction times between DMS (M = 243ms, SD = 48.1) and DNMS (M = 312ms, SD = 58.7), however, were significantly different (**t**(0.025,13) = -9.924; p = 0.001) with DNMS taking longer.

In an in-depth analysis of DNMS trials, results showed that the average saccade latency for targets that lie greater than 8^o degrees of visual angle from the forbidden location (M = 303, SD = 53.0) was significantly faster than the average saccade latency for targets that lie less than or equal to 8^o degrees of visual angle from the forbidden location (M = 317, SD = 62.2); (**t**(0.025,13) = 2.533; p = 0.025). Also, both of these latency values were significantly longer than the average latency value for DMS (M = 243, SD = 48.1); $\mathbf{t}_{\mathbf{> 8\ degrees}}(0.025,13) = 2.700$, p = 0.018; $\mathbf{t}_{\mathbf{< 8\ degrees}}(0.025,13) = 3.114$, p = 0.008.

Similar analyses were conducted for targets that, in respect to the forbidden stimulus, lie in 1) the same or opposite visual hemisphere and 2) in an adjacent or non-adjacent position. Neither of these analyses were significant.

FMRI Data

Results from the whole-brain analyses of both DMS/DNMS runs (concatenated to increase BOLD signal power) are shown in Figure 3.1. One-sample t-tests revealed significant differences in activity between DMS and DNMS trials in several regions (see Table 3.1). The regions that showed greater activity in the DNMS task when compared to the DMS task were the supplementary eye field (BA 6 in the superior frontal gyrus), the right medial frontal eye field (BA 6 in the precentral gyrus), bilateral and medial precuneus (BA 7 of the superior parietal lobule), and bilateral cuneus (BA 18/19 of the middle occipital gyrus) (see Figure 3.2). The regions that showed greater activity in the DMS task when compared to the DNMS task were medial regions around the cingulate gyrus (BA 24 and BA 31), a bilateral area near the precentral gyrus (near BA 4 (left) and BA 13 (right)), and several distinct areas of the prefrontal cortex (bilateral superior frontal gyrus (BA 8) and medial anterior prefrontal cortex (BA 10)) (see Figure 3.3). These fourteen areas comprised the regions of interest for the current study.

See Figures 3.4 and 3.5 for percent signal change bar graphs associated with DMS and DNMS, respectively.

Also, when comparing the two task runs, two regions revealed significantly greater DNMS activity during the second run; putamen (left lentiform nucleus) and an area in the left middle temporal gyrus. During the first run, activation of these regions was associated with DMS, but during run two, activation was associated with DNMS.

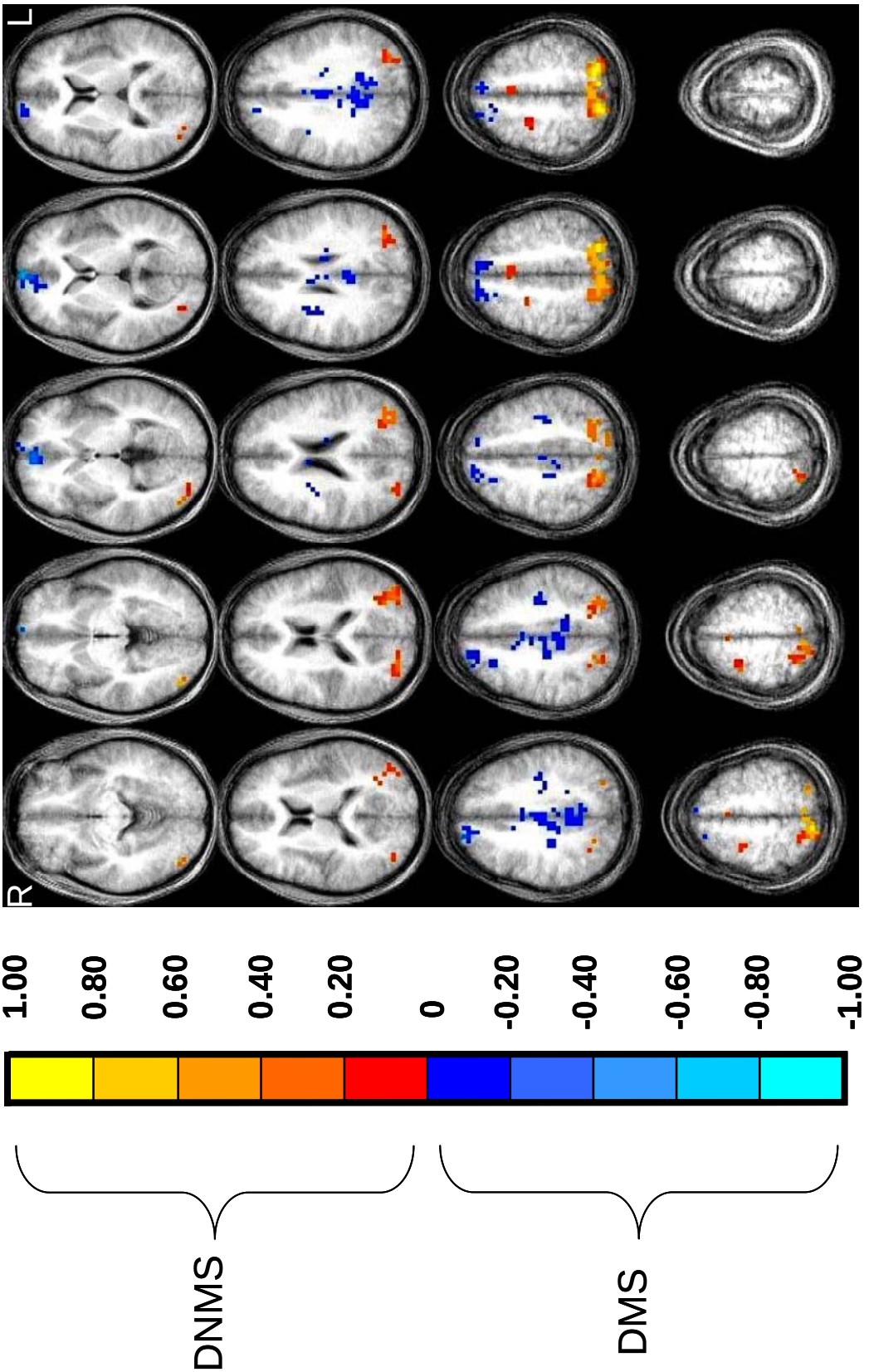
L
R
1.00
0.80
0.60
0.40
0.20
0
-0.20
-0.40
-0.60
-0.80
-1.00
DNMS
DMS

Figure 3.1 BOLD Activity Associated with DMS/DNMS Task
Axial slices (top left z = -6 through bottom right z = 70, spacing = 4mm) displaying significant BOLD signal changes between DMS and DNMS, concatenated across two runs. Areas associated with DNMS are shown in warm colors and areas associated with DMS are shown in cool colors. The background anatomical image is a structural image averaged over 13 participants and is shown using radiological convention. BOLD, blood oxygenation level-dependent; DMS, delayed-match-to-sample; DNMS, delayed-non-match-to-sample.

Table 3.1 Talairach Coordinates of the Centers of Mass for ROIs.
Regions represent areas that showed significant differences in BOLD signal between the DMS blocks and DNMS blocks.

ROIs with greater activation during the DNMS task	**L/R**	**X**	**Y**	**Z**
SEF, superior frontal gyrus (BA 6)		-2	+9	+51
Medial FEF, right precentral gyrus (BA 6)	R	+26	-6	+55
Precuneus, superior parietal lobule (BA 7)	R	+14	-68	+51
	L	-23	-66	+52
Cuneus, middle occipital gyrus (BA 18/19)	R	+31	-79	+20
	L	-32	-70	+24
Middle Occipital Gyrus (BA 18/19)	R	+37	-80	+2

ROIs with greater activation during the DMS task	**L/R**	**X**	**Y**	**Z**
Cingulate Gyrus (BA 24)		+2	-20	+36
Cingulate Gyrus (BA 31)		+2	-45	+33
Near Precentral Gyrus (BA 4)	L	-33	-18	+40
Near Precentral Gyrus (BA 13)	R	+32	-5	+26
Superior Frontal Gyrus (BA 8)	R	+15	+45	+38
	L	-7	+36	+50
Superior Frontal Gyrus (BA 10)		+4	+56	+7

ROI, region of interest; BOLD, blood oxygenation level-dependent; DMS, delayed-match-to-sample; DNMS, delayed-non-match-to-sample; SEF, supplementary eye fields; BA, Brodmann area; FEF, frontal eye fields.

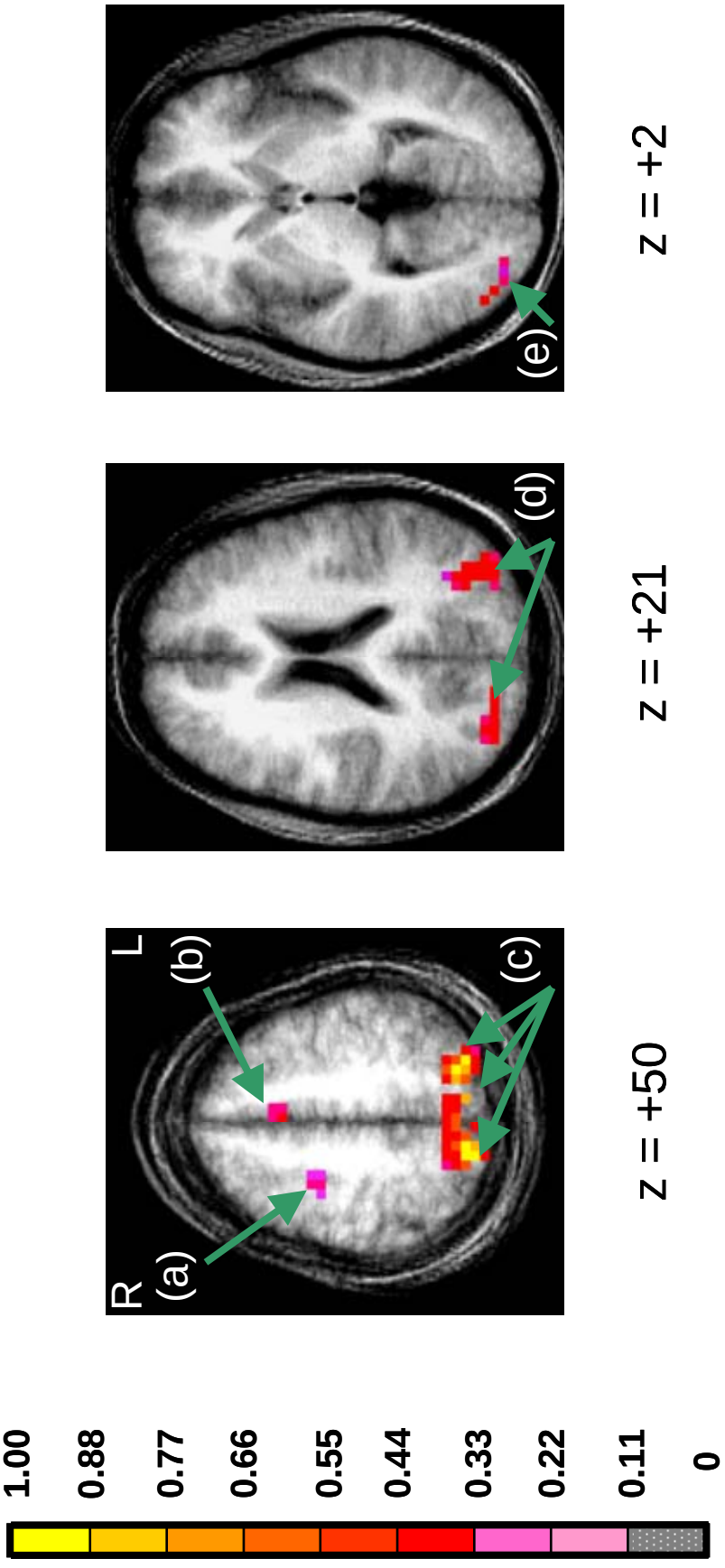
z = +50
z = +21
z = +2
R
L
(a)
(b)
(c)
(d)
(e)
1.00
0.88
0.77
0.66
0.55
0.44
0.33
0.22
0.11
0

Figure 3.2 BOLD Activity Associated with DNMS

Axial views displaying significant BOLD signal change associated with DNMS performance from one-sample t-test results. Data from 13 participants, concatenated across two task runs, are shown. Green arrows indicate: (a) right medial FEF, (b) SEF, (c) bilateral and medial precuneus, (d) bilateral cuneus, and (e) middle occipital gyrus. Colors from pink to yellow indicate percent signal change. The background is an anatomical image averaged over 13 participants and is shown using radiological convention. BOLD, blood oxygenation level-dependent; DNMS, delayed-non-match-to-sample; FEF, frontal eye fields; SEF, supplementary eye fields.

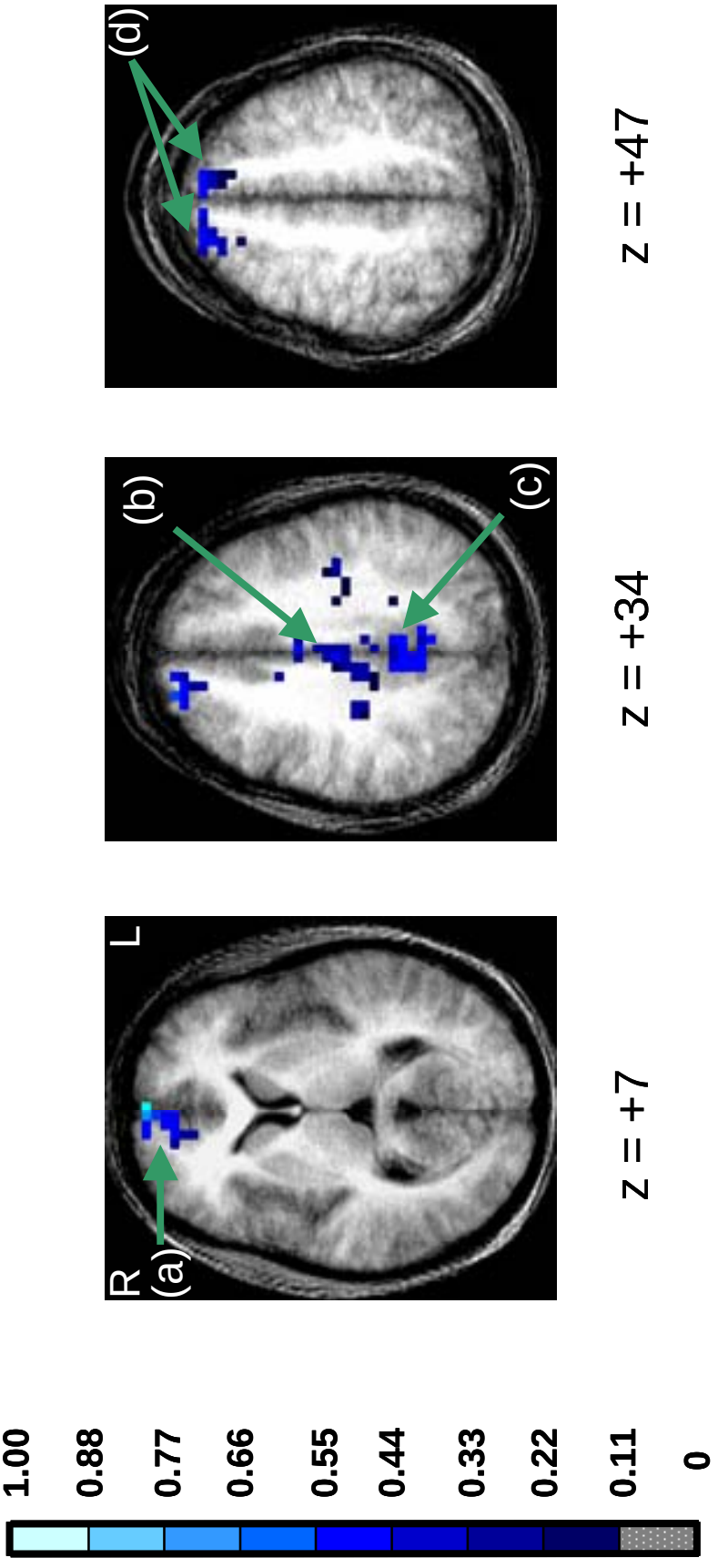
(d)
z = +47
(b)
(c)
z = +34
L
R
(a)
z = +7
1.00
0.88
0.77
0.66
0.55
0.44
0.33
0.22
0.11
0

Figure 3.3 BOLD Activity Associated with DMS

Axial views displaying BOLD signal change associated with DMS performance from one-sample t-test results. Data from 13 participants, concatenated across two task runs, are shown. Green arrows in indicate: (a) medial superior frontal gyrus (BA 10), (b) posterior ACC (BA 24), (c) cingulate gyrus (BA 31), and (d) bilateral superior frontal gyrus (BA 8). Colors from blue to white indicate percent signal change. The background is an anatomical image averaged over 13 participants and is shown using radiological convention. BOLD, blood oxygenation level-dependent; DMS, delayed-match-to-sample; BA, Brodmann area; ACC, anterior cingulate cortex.

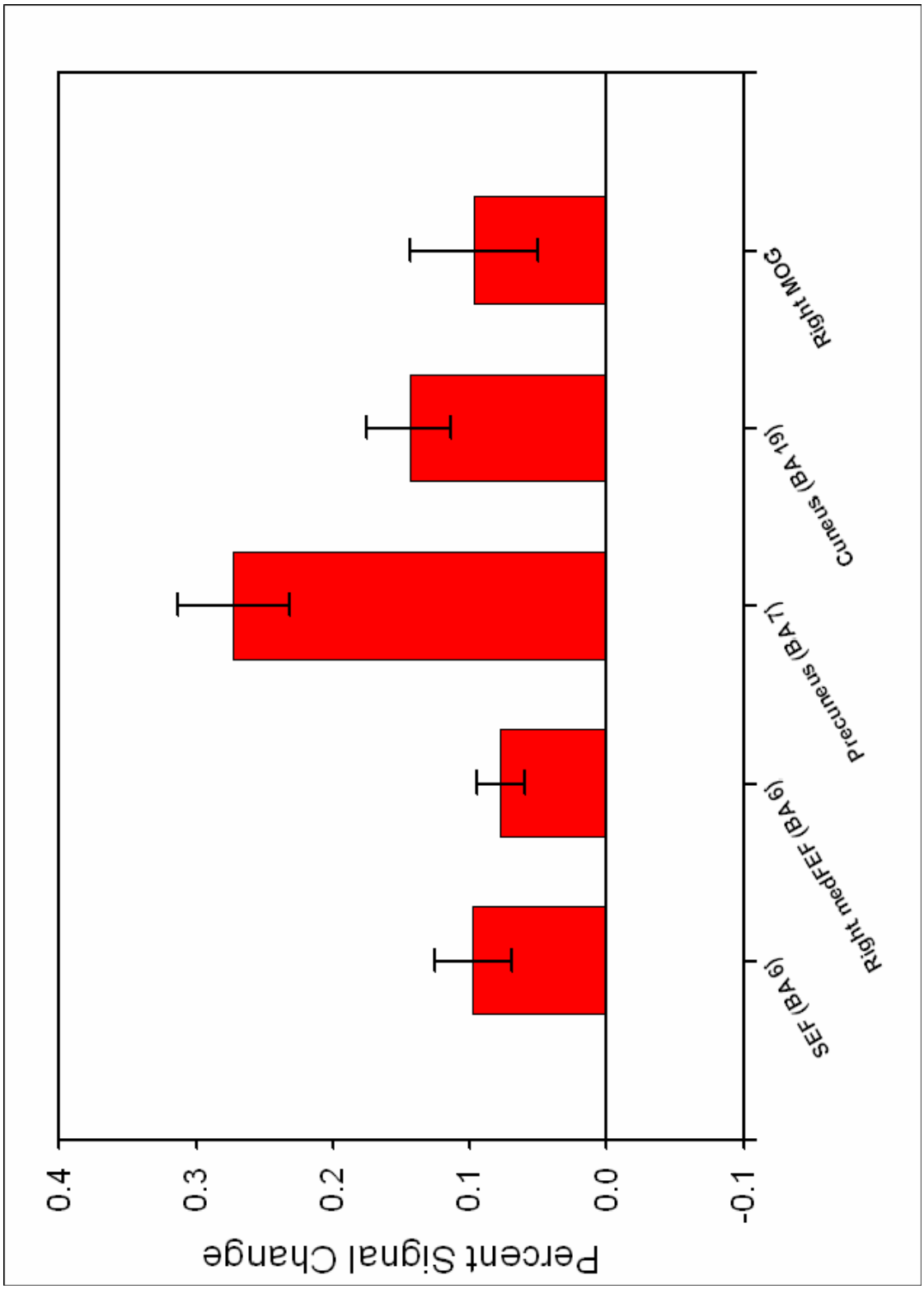

Figure 3.4 Percent Signal Change of ROIs Associated with DNMS

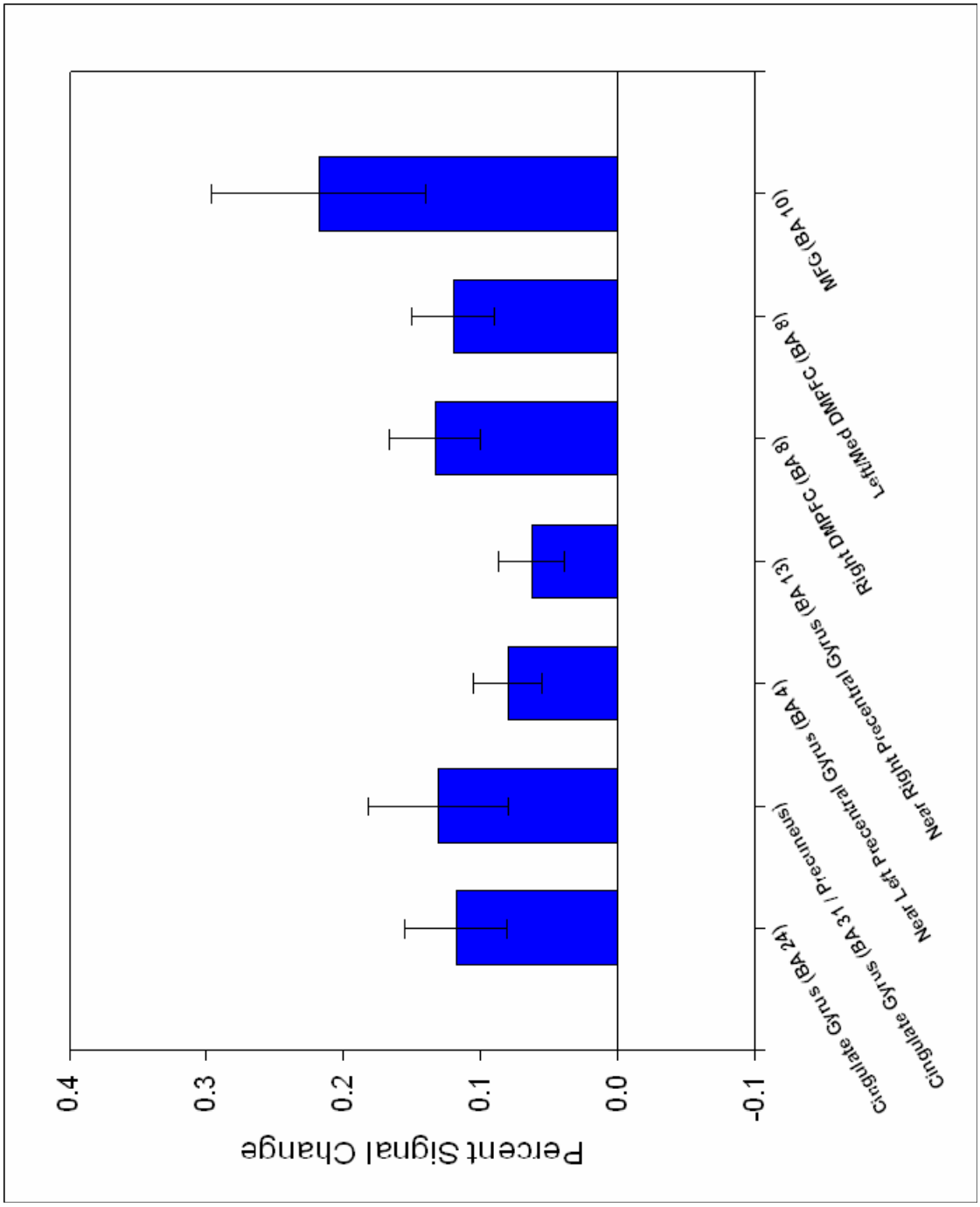

Figure 3.5 Percent Signal Change of ROIs Associated with DMS

CHAPTER 4

DISCUSSION

The present study investigated the neural substrates underlying delayed-match- (DMS) and delayed-non-match-to-sample (DNMS) saccades in humans using the modified Hasegawa DMS/DNMS task (Hasegawa et al., 2004). In the original study, Hasegawa et al. (2004) measured electrical activity of single neurons in the FEF and pre-FEF of two rhesus monkeys performing a DMS/DNMS task and described "look" and "don't look" prefrontal neurons that carried signals selective for the targeted or forbidden stimulus, respectively. The activity of these neurons correlated with the monkeys' success or failure on the task (Hasegawa et al., 2004). In the current study, the behavioral results showed DNMS latencies were significantly longer than for DMS. An analysis of DNMS saccade latencies also revealed that saccades to targets next to forbidden stimuli were slower than to those further away. Functional imaging results revealed a) greater DNMS-related activity in right medial frontal eye field (FEF), supplementary eye field (SEF), bilateral precuneus, and bilateral cuneus and b) greater DMS-related activity in cingulate gyrus, precentral gyrus, and two areas of prefrontal cortex (PFC) – BA 8 and BA 10.

Behavioral Measures

Task performance was consistent across runs. DMS saccade latencies and percentage of correct trials did not differ significantly between Run #1 and Run #2, and the same was observed for DNMS trials. When data were collapsed across the runs, analyses revealed that DMS and

DNMS did not differ significantly in the percentage of error trials, but they did differ in average saccade latencies – reaction times were significantly slower for DNMS than for DMS.

In the original study in monkeys, Hasegawa et al. (2004) found no significant differences in performance error, saccade latency, or velocity between DMS and DNMS trials. That adult humans in the current study showed greater saccade latencies for DNMS compared to DMS may be attributable to the strategies used during these tasks (Elliot and Dolan, 1999). A discussion of these strategies and task differences is discussed below in reference to functional imaging data.

FMRI Session

Neural Circuitry Differences Between DMS and DNMS

The imaging data suggest that the neural circuitry supporting DMS performance differs from the neural circuitry supporting DNMS performance. Compared to the DMS baseline, DNMS showed increased BOLD signal change in regions of the frontal and posterior parietal cortices known to support volitional eye movements. These areas included right medial frontal eye field (FEF), supplementary eye field (SEF), bilateral and medial precuneus (BA 7), and bilateral cuneus (BA 18/19) (Brown et al., 2004; Luna et al., 2002; Sweeney et al., 2007) (see Figure 3.2). DMS was associated with increased BOLD signal change in cortical areas including precentral gyrus, two regions of the cingulate gyrus (BA 24 and BA 31), and two regions in anterior prefrontal cortex (BA 10 and BA 8) (see Figure 3.3).

Interpreting the differences in brain activation suggested by functional imaging requires a closer look at the cognitive demands of the Hasegawa DMS/DNMS ocular motor paradigm. Successful performance on either task requires 1) the processing of rule-based behavior, 2) spatial attention, 3) saccadic inhibition to a flashing stimulus, 4) the maintenance of spatial location over a prescribed delay period, and 5) the generation of one saccade while

simultaneously inhibiting another. While DMS and DNMS share common cognitive processes, they are, however, inherently different on both behavioral and neural levels as suggested by the current results and similar studies (Hasegawa et al., 2004; Elliot & Dolan, 1999).

One of the main components of the Hasegawa DMS/DNMS task is the processing and implementation of rule-based behavior. Both DMS and DNMS require initial fixation on a central target that holds behavioral relevance. In the current paradigm, a fixation cross surrounded by a box denoted a DMS trial and a fixation cross surrounded by a diamond denoted a DNMS trial. Previous studies suggest that the prefrontal cortex is a critical component of the circuitry underlying rule-based behavior (Bunge et al., 2003), stimulus-response associations, and the implementation of task context (Johnston and Everling, 2006). In non-human primates, lesion studies have confirmed the importance of PFC for rule-guided behavior (Parker and Gaffan, 1998; Passingham, 1993; Petrides, 1985) and electrophysiological studies have shown that individual PFC neurons exhibit rule-sensitive activity (Asaad et al., 1998; White and Wise 1999).

In humans, neuroimaging studies indicate that activation in lateral PFC is associated with the active maintenance of contextual knowledge used to guide subsequent behavior (Braver et al., 2002; MacDonald et al., 2000; Sakai and Passingham, 2003), and studies of prefrontal damage show that patients have difficulty implementing contextually appropriate rules (Comalli et al., 1962; Luria, 1966; Milner, 1963). In the Hasegawa task, both DMS and DNMS require the maintenance and implementation of two distinctly different rule-based behaviors, i.e., to remember the location of the sample cue as a marker of where to look (DMS) or where not to look (DNMS). There is evidence suggesting, however, that DNMS, for adult humans, may be cognitively more complex than DMS. A previous study investigating DMS and DNMS suggests

that, because of a natural tendency to respond to familiar stimuli, DNMS requires an additional processing stage - the inhibition of response to a familiar stimulus (Elliot and Dolan, 1999) and may be a more difficult task for adult humans. It should be noted, however, that in monkeys and human infants, the instinctive preference is for novel stimuli, and DMS is the more difficult task (Gaffan et al., 1984; Diamond, 1991) because it requires saccadic inhibition to the newly-appearing test cue. While this proposed difference in difficulty was not reflected in the behavioral results for the Hasegawa task in monkeys (Hasegawa et al., 2004), it is supported by the current behavioral results for adult humans (See Results section). These differences may also be reflected in the imaging data; the higher degree of complexity of DNMS may be reflected by increased activation in medial FEF, SEF, and PPC associated with the DNMS task. Previous studies report that these three areas, which are involved in saccade triggering (Pierrot-Deseilligny et al., 1995, 2002; Leigh and Zee, 1999), show increased activation for saccade tasks of higher complexity. For example, the cortical circuitry supporting antisaccades shows increased activation in FEF, SEF, and PPC when compared to basic prosaccades (e.g. Raemaekers et al., 2006a, b; Ford et al., 2005; Curtis and D'Esposito 2003; Luna et al., 2001; Doricchi et al., 1997; DeSouza et al., 2003). Thus, it is possible that increased activation in FEF, SEF, and PPC associated with DNMS may be associated with the higher degree of difficulty in the cognitive processes supporting DNMS. It is also possible, however, that the increased activation in each of these regions is attributable to the specific role of each region in the DNMS task.

The posterior parietal cortex is known to support the control of eye-movements (Camchong et al., 2006) and attention (Pierrot-Deseilligny et al., 2004). In DNMS, the greatest positive change in BOLD signal was observed in bilateral and medial precuneus (BA 7) in the

PPC. Activation in this region was widespread, extending bilaterally from medial superior parietal lobule (SPL) to the boundary of the intraparietal sulcus (IPS). The precuneus, as part of a network including the hippocampus, is implicated in the active maintenance of spatial associative information and may represent an interface between working memory areas in the PFC and the medial temporal lobe (Kobayashi and Amaral, 2003). The precuneus is also implicated in the retrieval of spatial and temporal information, such as episodic memory retrieval (Wagner et al., 2005). A previous neuroimaging study investigating the neural differences underlying DMS and DNMS task differences (in a non-spatial, button-press version of the paradigm) also reported that activation of the medial parietal cortex (precuneus, BA7) was associated with DNMS (Elliot and Dolan, 1999). In the current study, bilateral activation of this region associated with the non-match task may suggest that maintenance of spatial information was more active in DNMS than DMS. This difference may be attributable to the timing of the transformation from perception to action that distinguishes DMS and DNMS (Curtis et al., 2004). In DMS, the participant knows *a priori* that the location of the sample cue will be the target of the saccade, whereas, in DNMS, the target of the saccade is unpredictable. During the delay period, the participant is able to plan a motor response for DMS while, for DNMS, they can only store the location of the sample cue as a marker of where not to look. In this way, DMS requires the maintenance of a prospective motor code, or motor intention, and DNMS requires the maintenance of a retrospective memory code, or sustained spatial attention (Curtis et al., 2004). That DNMS requires greater sustained spatial attention than DMS may account for the increased activation of precuneus during DNMS performance.

The FEF in humans, located at the intersection between the precentral sulcus and the superior frontal sulcus (Pierrot-Deseilligny et al., 2004), are involved in the preparation and

triggering of all intentional saccades (e.g. Bruce and Goldberg, 1985; Rivaud et al., 1994; Pierrot-Deseilligny et al., 1991) including intentional visually guided saccades (where the target is present), memory-guided saccades (where the target is not present), and antisaccades (where the target is in the opposite direction of a cue) (Pierrot-Deseilligny et al., 2003b). Neuroimaging studies have consistently found greater activity in FEF 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). This increased activation (anti- compared to pro-saccade trials) has been observed specifically during the period prior to saccade generation (Clementz et al., 2007; Connolly et al., 2002; DeSouza et al., 2003; Ford et al., 2005; Manoach et al., 2007; McDowell et al., 2005), and 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).

For the current study, in which increased FEF activation was associated with DNMS, there are two possible implications; 1) that DNMS required a stronger inhibitory signal than DMS and 2) that the saccade generated during DNMS was more volitional in nature than the saccade generated during DMS. Both of these implications are plausible considering the strategy involved in the DMS/DNMS paradigm. As discussed previously, during the delay period, the participant is able to plan a motor response for DMS while, for DNMS, they can only store the location of the sample cue as a marker of where not to look. Increased FEF activation for DNMS may be attributable to this sustained inhibitory intention. Also, that DNMS saccades were intentionally generated may be related to the role of the FEF in the selection of competing saccade goals (Schall, 2002; Curtis and D'Esposito, 2006). This is also the case in the current

DNMS task where the subject must choose between two possible saccades, one of which is known to be an incorrect response. In DMS, however, there is no such competition or selection required; the saccade to the previously presented cue is planned over the delay period and the newly presented cue can more or less be disregarded. Thus, activation of the right medial FEF in DNMS is consistent with the role of the FEF in sustaining inhibitory intention, generating intentional saccades, and selecting between competing saccade goals.

The SEF is also implicated in ocular motor control (Müri et al., 1998) and is associated with DNMS. Located in the upper part of the paracentral sulcus (Grosbras et al., 1999), i.e., medially in the superior frontal gyrus (Pierrot-Deseilligny et al., 2003a), 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). The role of SEF in saccade tasks may be in cognitive control, specifically during generation of complex saccades (Parton et al., 2007; Stuphorn et al., 2000), such as antisaccades. Numerous single-unit recording (e.g. Amador et al., 2004; Schlag-Rey et al., 1997) and human neuroimaging studies (e.g. Clementz et al., 2007; Curtis & D'Esposito 2003, 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) have reported increased activation of SEF during antisaccades compared to prosaccades.

The repeated implication of SEF in tasks of higher complexity may explain increased activation of this region during DNMS. As discussed previously, DNMS is considered more complex than DMS because of an additional processing stage (the inhibition of response to a familiar stimulus) (Elliot and Dolan, 1999). This increased activation, however, may be better explained by the role of SEF in controlling response selection when faced with competing

saccade plans (Parton et al., 2007). For example, using a pro-/anti-saccade interleaved task, Parton et al. observed that a patient with a focal SEF lesion performed worse (more prosaccades errors, slower antisaccade latencies) than when prosaccades and antisaccades were presented separately. In the current paradigm, DNMS also requires competing saccade goals – "Look away from the forbidden stimulus and look at the newly presented cue". DMS does not involve such interfering saccade goals. Soon after the location of the sample cue is processed, the spatial information may be transformed into a prospective motor code (Curtis et al., 2004) – "Look at this location when the cross disappears" – that is not distracted by the newly appearing cue. The current behavioral results support this strategy - DMS latencies were significantly faster than DNMS latencies. Increased latencies in DNMS resulted from the extra time it took the participant to choose the correct response between two competing targets. Then, the participant had to inhibit one saccade and simultaneously generate another. These competing saccade goals may account for increased activation of SEF during DNMS.

DNMS was also associated with greater activity in middle occipital gyrus (BA 18/19), specifically bilateral 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). Increased activation of this area associated with DNMS may be attributable to a more effortful integration of spatial information resulting from competing saccades. As discussed previously, DMS strategy may involve transforming the location of the sample cue into a motor intention (a gaze). The transformation at this stage is relatively simple as there is only one location to which a gaze may be planned. In DNMS, however, the eye movement cannot be planned at this stage; the location of the correct response is still unknown. It is only during the test period, when the sample cue

(the incorrect response) and the new cue (the correct response) appear simultaneously, that a correct response can be determined. These competing targets require that both locations be integrated before the appropriate saccade can be commanded. Thus, increased activation of cuneus in DNMS may be explained by having to integrate and choose between two spatial locations while, in DMS, there is no such competition when planning the correct response.

Intentional and Reflexive Saccades in DNMS

Behavioral results show that, for DNMS, the average saccade latency for targets that lie further from the forbidden location was significantly faster than the average saccade latency for targets that lie closer to the forbidden location.

In an analysis that compared saccade latencies of correct targets in relation to their distance from the forbidden (sample) location, three categories were investigated; 1) targets that were in same or opposite hemisphere, 2) targets there were adjacent or non-adjacent, and 3) targets that were less or greater than 8^{o} from the forbidden location. For the first category, analyses revealed that saccade latencies did not differ for targets in same hemisphere and targets in the opposite hemisphere as the forbidden location. For targets that were adjacent to the forbidden location, however, saccade latencies were slower than for targets that were non-adjacent, though these results did not achieve significance. Finally, analyses revealed that for targets that were less than or equal to 8^{o} from the forbidden location, saccade latencies were significantly slower than for targets that were greater than 8^{o} from the forbidden location (see Results, Chapter 3). These behavioral results suggest that DNMS may involve two different mechanisms in generating saccades, depending on the location of the target to the forbidden stimulus. A closer look at the current imaging results may support this dissociation.

The current imaging results suggest that while DMS requires regions associated with the generation of intentional saccades, DNMS requires regions associated with both intentional and reflexive saccades.

The most widespread activation for DMS was observed in two regions of the cingulate gyrus – BA 24 and BA 31, the former of which is associated with the control of intentional saccades (see Figure 3.3). Activation of BA 24 is specific to the posterior portion of the anterior cingulate cortex (ACC), a region known as the cingulate eye field (CEF) (Pierrot-Deseilligny et al., 2004). Previous studies report that CEF may be specifically involved in the control of intentional saccades but not reflexive saccades (Gaymard et al., 1998) and may play a role, via an early motivational process, in preparing all frontal ocular motor areas involved in intentional saccade control to act in the forthcoming motor behavior (Pierrot-Deseilligny et al., 2004). That DMS involves a planned motor response (a volitionally-generated gaze) to the location of the sample cue is supported by the implication of CEF in the control of intentional saccades (Gaymard et al., 1998).

For DNMS, however, we observe activation in regions associated with generating intentional saccades and regions associated with generating reflexive saccades. As discussed previously, DNMS showed increased activation of FEF which is consistent with the role of the FEF in sustaining inhibitory intention, generating intentional saccades, and selecting between competing saccade goals. This activation, however, was specific to right medial FEF, a region associated specifically with volitional, but not reflexive saccades (Gagnon et al., 2002; Simó et al., 2005). During the same task, however, we also observe increased BOLD signal in a region implicated in the generation of reflexive saccades – the parietal eye field (PEF). This region of the posterior parietal cortex lie in the posterior portion of the intraparietal sulcus (Müri et al.,

1996), adjacent laterally to the anterior part of the angular gyrus (BA 39) and adjacent medially to the posterior part of the superior parietal lobule (BA 7) (Kawashima et al., 1996a; Büchel et al., 1998; Simon et al., 2002; Culham and Kanwisher, 2001; Brotchie et al., 2003; Macaluso et al., 2003). Previous studies report that the PEF is involved in visuo-spatial integration (Pierrot-Deseilligny et al., 2004) and is crucial for the generation of reflexive, but not intentional, saccades (Pierrot-Deseilligny et al., 1991).

This dissociation suggests that DNMS may involve reflexive saccades for some trials and intentional saccades for others. It is possible that error trials (in which the participant is reflexively guided towards the incorrect target) are responsible for increased activity in PEF, but this is unlikely, since participants performed 92.5% (SD = 9.2) of all DNMS trials correctly. Instead, DNMS performance may involve two separate mechanisms for generating a correct response – a primary reflexive mechanism (fostered by PEF) and a secondary intentional mechanism (fostered by the medial FEF).

The orientation of the target to the inhibited location may determine whether the gaze generated is more reflexive or intentional in nature. Behavioral results show that, in DNMS, when targets lie far away from the inhibited area (i.e., more than 8^{o}), saccades were generated with faster latencies than if the target lie close in proximity to the inhibited location (i.e., less than 8^{o} apart). Perhaps, as a primary mechanism, the PEF is primed to allow gazes to be reflexively guided to targets far away from the forbidden location. If the target happens to be close to the forbidden location, however, the saccade goals compete with one another, and a correct (intentional) gaze must be chosen. This secondary mechanism is consistent with the role of medial FEF in the generation of intentional saccades and selecting between competing

saccade goals. The selection process, as a higher-order cognitive function, may account for the increased latency associated with saccades closer to the forbidden stimulus.

Activation of Anterior Prefrontal Cortex in DMS

DMS revealed a significant increase in BOLD signal, compared to DNMS, in the anterior prefrontal cortex. This frontal pole region, or Brodmann Area 10, has equivocal contributions to cognition, ranging from the processing of internal states (Christoff and Gabrieli, 2000), memory retrieval models (Tulving, 1983), prospective memory (Burgess et al., 2001), the branching and reallocation of attention (Koechlin et al., 1999, 2000), and relational integration (Christoff et al., 2001). The current results support the role of BA 10 in prospective memory, and perhaps, more specifically, in prospective memory tasks involving motor acts.

According to Ramnani and Owen (2004), situations that require prospective memory involve a period of delay, an intended act, an ongoing task during the delay period (typically unrelated to the intended act), and a trigger to self initiate the planned activity. In the Hasegawa paradigm, these attributes of prospective memory are shared by both DMS and DNMS - once the location of the sample cue is processed, the subject plans an intended act, maintains this plan over a delay period while fixating on central target, and finally initiates the act when triggered by the extinction of the fixation target. The nature of the intended act - to generate a saccade to the location of the cue (DMS) or to inhibit a saccade to the location of cue (DNMS) - however, is a distinguishing difference between the two tasks, and may account for the increased BOLD signal in DMS.

The current imaging results suggest that DNMS requires a lesser contribution from BA 10, but, more liberally, could also imply that DNMS does not require any contribution from BA 10. Previous studies investigating the role of BA 10 in prospective memory have only studied

motor acts as the intended act – not as an inhibited one. For example, a PET study using prospective memory tasks that required a button press as the intended act reported increased regional blood flow in bilateral frontal pole (Burgess et al., 2001). Also, in a study with five patients with frontal lobe lesions that included the anterior PFC, cognitive deficits included failure to create and carry out intended acts (Burgess et al., 2000). Thus, the current results support the role of the frontal pole, BA 10, in prospective memory, and imply that its contribution may be specific to planned motor acts and not the planned inhibition of motor acts.

DMS was also associated with increased activation in superior frontal gyrus (SFG), specifically BA 8. SFG is thought to contribute to higher-level cognitive functions and particularly to working memory (du Boisgueheneuc et al., 2006). In the current study, it is unlikely that increased SFG activation in DMS is associated with higher-level cognitive demands when compared to DNMS; previous studies (Elliot and Dolan, 1999) and the behavioral results indicate that DNMS is the more complex task (DNMS had significantly longer latencies). Instead, it is more likely the increased activation is attributed to a stronger working memory signal required by DMS. As discussed previously, DMS strategy may involve maintaining a planned motor intention over the delay period while DNMS strategy may involve maintaining a planned inhibition over the delay period. Thus, the current results may imply that working memory associated with a motor intention requires more resources from SFG than does working memory associated with inhibition intention.

DMS also shows significant activation in two areas of the precentral gryrus (BA 4 and BA 13). This area corresponds to the primary motor cortex which governs the execution of volitional movement. In DMS, the plan to execute a gaze to a specific location is generated upon appearance of the sample cue and is maintained over the delay period. The temporal span of the

maintenance of this motor code is large compared to that of DNMS, in which the gaze is executed instantaneously after a correct response is chosen. Thus, activation of precentral gyrus may increase with longer periods of motor code maintenance, as exemplified in the DMS task.

Conclusions

The behavioral and fMR imaging techniques used in the current study complemented each other to yield information about the neural substrates supporting DMS and DNMS task performance. DMS activity was observed in cingulate cortex, anterior prefrontal cortex, and precentral gyrus. Activation of these areas may support the cognitive processes necessary for maintaining prospective and working memory of an intended motor act and executing an intentional saccade. DNMS activity was observed in regions known to support the generation of saccades, particularly voluntary saccades, including medial FEF, SEF, precuneus, and cuneus. Activation of this circuitry is consistent with its role in maintaining spatial information, and deciding between competing saccade goals. Also, activation of right medial FEF, specifically, may be the human analogue of the "don't look" signal described in the pre-FEF and FEF by Hasegawa et al. (2004). Behavioral results revealed that for DNMS trials, saccade latencies for targets further from the forbidden stimulus were significantly faster than for targets closer to the forbidden location. The imaging data suggest that this difference may be the result of separate mechanisms involved in generating reflexive and intentional saccades – a primary reflexive mechanism in PEF and a secondary intentional mechanism in medial FEF.

REFERENCES

Amador, N., Schlag-Rey, M., & Schlag, J. (2004). Primate antisaccade. II. Supplementary eye field neuronal activity predicts correct performance. *J Neurophysiol, 91*(4), 1672-1689.

Asaad, W. F., Rainer, G., & Miller, E. K. (1998). Neural activity in the primate prefrontal cortex during associative learning. *Neuron, 21*(6), 1399-1407.

Bizzi, E. (1967). Discharge of frontal eye field neurons during eye movements in unanesthetized monkeys. *Science, 157*(796), 1588-1590.

Braver, T., Cohen, J., & Barch, D. (2002). The role of prefrontal cortex in normal and disordered cognitive control: a cognitive neuroscience perspective. In S. Knight (Ed.), *Principles of Frontal Lobe Function* (pp. 428-447). New York: Oxford.

Brotchie, P. R., Lee, M. B., Chen, D. Y., Lourensz, M., Jackson, G., & Bradley, W. G., Jr. (2003). Head position modulates activity in the human parietal eye fields. *Neuroimage, 18*(1), 178-184.

Brown, M. R., DeSouza, J. F., Goltz, H. C., Ford, K., Menon, R. S., Goodale, M. A., et al. (2004). Comparison of memory- and visually guided saccades using event-related fMRI. *J Neurophysiol, 91*(2), 873-889.

Bruce, C. J., & Goldberg, M. E. (1985). Primate frontal eye fields. I. Single neurons discharging before saccades. *J Neurophysiol, 53*(3), 603-635.

Buchel, C., Josephs, O., Rees, G., Turner, R., Frith, C. D., & Friston, K. J. (1998). The functional anatomy of attention to visual motion. A functional MRI study. *Brain, 121 (Pt 7)*, 1281-1294.

Bunge, S. A., Kahn, I., Wallis, J. D., Miller, E. K., & Wagner, A. D. (2003). Neural circuits subserving the retrieval and maintenance of abstract rules. *J Neurophysiol, 90*(5), 3419-3428.

Burgess, P. W., Quayle, A., & Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia, 39*(6), 545-555.

Burgess, P. W., Veitch, E., de Lacy Costello, A., & Shallice, T. (2000). The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia, 38*(6), 848-863.

Camchong, J., Dyckman, K. A., Chapman, C. E., Yanasak, N. E., & McDowell, J. E. (2006). Basal ganglia-thalamocortical circuitry disruptions in schizophrenia during delayed response tasks. *Biol Psychiatry, 60*(3), 235-241.

Casey, B. J., Castellanos, F. X., Giedd, J. N., Marsh, W. L., Hamburger, S. D., Schubert, A. B., et al. (1997). Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry, 36*(3), 374-383.

Christoff, K., & Gabrieli, J. D. E. (2000). The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology*.

Christoff, K., Prabhakaran, V., Dorfman, J., Zhao, Z., Kroger, J. K., Holyoak, K. J., et al. (2001). Rostrolateral prefrontal cortex involvement in relational integration during reasoning. *Neuroimage, 14*(5), 1136-1149.

Clementz, B. A., Brahmbhatt, S. B., McDowell, J. E., Brown, R., & Sweeney, J. A. (2007). When Does the Brain Inform the Eyes Whether and Where to Move? an EEG Study in Humans. *Cereb Cortex*.

Comalli, P. E., Jr., Wapner, S., & Werner, H. (1962). Interfernce effects of Stroop color-word test in childhood, adulthood, and aging. *J Genet Psychol, 100*, 47-53.

Connolly, J. D., Goodale, M. A., Menon, R. S., & Munoz, D. P. (2002). Human fMRI evidence for the neural correlates of preparatory set. *Nat Neurosci, 5*(12), 1345-1352.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res, 29*(3), 162-173.

Culham, J. C., & Kanwisher, N. G. (2001). Neuroimaging of cognitive functions in human parietal cortex. *Curr Opin Neurobiol, 11*(2), 157-163.

Curtis, C. E., & D'Esposito, M. (2003). Success and failure suppressing reflexive behavior. *J Cogn Neurosci, 15*(3), 409-418.

Curtis, C. E., & D'Esposito, M. (2006). Selection and maintenance of saccade goals in the human frontal eye fields. *J Neurophysiol, 95*(6), 3923-3927.

Curtis, C. E., Rao, V. Y., & D'Esposito, M. (2004). Maintenance of spatial and motor codes during oculomotor delayed response tasks. *J Neurosci, 24*(16), 3944-3952.

DeSouza, J. F., Menon, R. S., & Everling, S. (2003). Preparatory set associated with pro-saccades and anti-saccades in humans investigated with event-related FMRI. *J Neurophysiol, 89*(2), 1016-1023.

Diamond, A. (1991). Guidelines for the study of brain-behaviour relationships during development. In H. Levin, H. Eisenberg & A. Benton (Eds.), *Frontal lobe function and dysfunction* (pp. 339-380). Oxford: Oxford UP.

Doricchi, F., Perani, D., Incoccia, C., Grassi, F., Cappa, S. F., Bettinardi, V., et al. (1997). Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography. *Exp Brain Res, 116*(1), 50-62.

du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., et al. (2006). Functions of the left superior frontal gyrus in humans: a lesion study. *Brain, 129*(Pt 12), 3315-3328.

Dyckman, K. A., Camchong, J., Clementz, B. A., & McDowell, J. E. (2007). An effect of context on saccade-related behavior and brain activity. *Neuroimage, 36*(3), 774-784.

Elliott, R., & Dolan, R. J. (1999). Differential neural responses during performance of matching and nonmatching to sample tasks at two delay intervals. *J Neurosci, 19*(12), 5066-5073.

Fischer, B., Weber, H., Biscaldi, M., Aiple, F., Otto, P., & Stuhr, V. (1993). Separate populations of visually guided saccades in humans: reaction times and amplitudes. *Exp Brain Res, 92*(3), 528-541.

Ford, J. M., Gray, M., Whitfield, S. L., Turken, A. U., Glover, G., Faustman, W. O., et al. (2004). Acquiring and inhibiting prepotent responses in schizophrenia: event-related brain potentials and functional magnetic resonance imaging. *Arch Gen Psychiatry, 61*(2), 119-129.

Ford, K. A., Goltz, H. C., Brown, M. R., & Everling, S. (2005). Neural processes associated with antisaccade task performance investigated with event-related FMRI. *J Neurophysiol, 94*(1), 429-440.

Gaffan, D., Gaffan, E. A., & Harrison, S. (1984). Effects of fornix transection on spontaneous and trained non-matching by monkeys. *Q J Exp Psychol B, 36*(4), 285-303.

Gagnon, D., O'Driscoll, G. A., Petrides, M., & Pike, G. B. (2002). The effect of spatial and

temporal information on saccades and neural activity in oculomotor structures. *Brain, 125*(Pt 1), 123-139.

Gandhi, N. J., & Keller, E. L. (1999). Comparison of saccades perturbed by stimulation of the rostral superior colliculus, the caudal superior colliculus, and the omnipause neuron region. *J Neurophysiol, 82*(6), 3236-3253.

Gaymard, B., Ploner, C. J., Rivaud-Pechoux, S., & Pierrot-Deseilligny, C. (1999). The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Exp Brain Res, 129*(2), 288-301.

Gaymard, B., Rivaud, S., Cassarini, J. F., Dubard, T., Rancurel, G., Agid, Y., et al. (1998). Effects of anterior cingulate cortex lesions on ocular saccades in humans. *Exp Brain Res, 120*(2), 173-183.

Glover, G. H., & Lai, S. (1998). Self-navigated spiral fMRI: interleaved versus single-shot. *Magn Reson Med, 39*(3), 361-368.

Goldberg, M. E., Bushnell, M. C., & Bruce, C. J. (1986). The effect of attentive fixation on eye movements evoked by electrical stimulation of the frontal eye fields. *Exp Brain Res, 61*(3), 579-584.

Grosbras, M. H., Lobel, E., Van de Moortele, P. F., LeBihan, D., & Berthoz, A. (1999). An anatomical landmark for the supplementary eye fields in human revealed with functional magnetic resonance imaging. *Cereb Cortex, 9*(7), 705-711.

Guitton, D., Buchtel, H. A., & Douglas, R. M. (1985). Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res, 58*(3), 455-472.

Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Res, 18*(10), 1279-1296.

Hasegawa, R. P., Peterson, B. W., & Goldberg, M. E. (2004). Prefrontal neurons coding suppression of specific saccades. *Neuron, 43*(3), 415-425.

Hikosaka, O., & Wurtz, R. H. (1983). Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. *J Neurophysiol, 49*(5), 1268-1284.

Iversen, S. D., & Mishkin, M. (1970). Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Exp Brain Res, 11*(4), 376-386.

Iwabuchi, A., & Kubota, K. (1998). Laminar organization of neuronal activities in area 8 of rhesus monkeys during a symmetrically reinforced visual GO/NO-GO task. *Int J Neurosci, 94*(1-2), 1-25.

Johnston, K., & Everling, S. (2006). Neural activity in monkey prefrontal cortex is modulated by task context and behavioral instruction during delayed-match-to-sample and conditional prosaccade-antisaccade tasks. *J Cogn Neurosci, 18*(5), 749-765.

Kawashima, R., Naitoh, E., Matsumura, M., Itoh, H., Ono, S., Satoh, K., et al. (1996a). Topographic representation in human intraparietal sulcus of reaching and saccade. *Neuroreport, 7*(7), 1253-1256.

Kawashima, R., Satoh, K., Itoh, H., Ono, S., Furumoto, S., Gotoh, R., et al. (1996b). Functional anatomy of GO/NO-GO discrimination and response selection--a PET study in man. *Brain Res, 728*(1), 79-89.

Kiefer, M., Marzinzik, F., Weisbrod, M., Scherg, M., & Spitzer, M. (1998). The time course of brain activations during response inhibition: evidence from event-related potentials in a go/no go task. *Neuroreport, 9*(4), 765-770.

Kimmig, H., Greenlee, M. W., Gondan, M., Schira, M., Kassubek, J., & Mergner, T. (2001). Relationship between saccadic eye movements and cortical activity as measured by fMRI: quantitative and qualitative aspects. *Exp Brain Res, 141*(2), 184-194.

Kobayashi, Y., & Amaral, D. G. (2003). Macaque monkey retrosplenial cortex: II. Cortical afferents. *J Comp Neurol, 466*(1), 48-79.

Koechlin, E., Basso, G., Pietrini, P., Panzer, S., & Grafman, J. (1999). The role of the anterior prefrontal cortex in human cognition. *Nature, 399*(6732), 148-151.

Koechlin, E., Corrado, G., Pietrini, P., & Grafman, J. (2000). Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. *Proc Natl Acad Sci U S A, 97*(13), 7651-7656.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain, 122 (Pt 5)*, 981-991.

Konishi, S., Nakajima, K., Uchida, I., Sekihara, K., & Miyashita, Y. (1998). No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. *Eur J Neurosci, 10*(3), 1209-1213.

Leigh, R. J., & Zee, D. S. (1999). *The neurology of eye movements* (3rd ed.). New York ; Oxford: Oxford University Press.

Leung, H. C., Gore, J. C., & Goldman-Rakic, P. S. (2002). Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda. *J Cogn Neurosci, 14*(4), 659-671.

Li, B. M., & Kubota, K. (1998). Alpha-2 adrenergic modulation of prefrontal cortical neuronal activity related to a visual discrimination task with GO and NO-GO performances in monkeys. *Neurosci Res, 31*(2), 83-95.

Luna, B., Minshew, N. J., Garver, K. E., Lazar, N. A., Thulborn, K. R., Eddy, W. F., et al. (2002). Neocortical system abnormalities in autism: an fMRI study of spatial working memory. *Neurology, 59*(6), 834-840.

Luna, B., Thulborn, K. R., Munoz, D. P., Merriam, E. P., Garver, K. E., Minshew, N. J., et al. (2001). Maturation of widely distributed brain function subserves cognitive development. *Neuroimage, 13*(5), 786-793.

Luria, A. (1966). *Higher Cortical Functions in Man*. New York: Basic Books.

Lynch, J. C., & Tian, J. R. (2005). Cortico-cortical networks and cortico-subcortical loops for the higher control of eye movements. *Prog Brain Res, 151*, 461-501.

Macaluso, E., Driver, J., & Frith, C. D. (2003). Multimodal spatial representations engaged in human parietal cortex during both saccadic and manual spatial orienting. *Curr Biol, 13*(12), 990-999.

MacDonald, A. W., 3rd, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*(5472), 1835-1838.

Manoach, D. S., Thakkar, K. N., Cain, M. S., Polli, F. E., Edelman, J. A., Fischl, B., et al. (2007). Neural activity is modulated by trial history: a functional magnetic resonance imaging study of the effects of a previous antisaccade. *J Neurosci, 27*(7), 1791-1798.

Matsuda, T., Matsuura, M., Ohkubo, T., Ohkubo, H., Matsushima, E., Inoue, K., et al. (2004). Functional MRI mapping of brain activation during visually guided saccades and antisaccades: cortical and subcortical networks. *Psychiatry Res, 131*(2), 147-155.

McDowell, J. E., Brown, G. G., Paulus, M., Martinez, A., Stewart, S. E., Dubowitz, D. J., et al.

(2002). Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol Psychiatry, 51*(3), 216-223.

McDowell, J. E., Kissler, J. M., Berg, P., Dyckman, K. A., Gao, Y., Rockstroh, B., et al. (2005). Electroencephalography/magnetoencephalography study of cortical activities preceding prosaccades and antisaccades. *Neuroreport, 16*(7), 663-668.

Mendelson, M. J., Mendelson, M. J., Haith, M. M., & Goldman-Rakic, P. S. (1982). Face scanning and responsiveness to social cues in infant rhesus monkeys. *Developmental Psychology*.

Milea, D., Lobel, E., Lehericy, S., Pierrot-Deseilligny, C., & Berthoz, A. (2005). Cortical mechanisms of saccade generation from execution to decision. *Ann N Y Acad Sci, 1039*, 232-238.

Milner, B. (1963). Effects of different brain lesions on card sorting. *Arch Neurol, 9*, 90-100.

Munoz, D. P., & Wurtz, R. H. (1993). Fixation cells in monkey superior colliculus. I. Characteristics of cell discharge. *J Neurophysiol, 70*(2), 559-575.

Muri, R. M., Heid, O., Nirkko, A. C., Ozdoba, C., Felblinger, J., Schroth, G., et al. (1998). Functional organisation of saccades and antisaccades in the frontal lobe in humans: a study with echo planar functional magnetic resonance imaging. *J Neurol Neurosurg Psychiatry, 65*(3), 374-377.

Muri, R. M., Iba-Zizen, M. T., Derosier, C., Cabanis, E. A., & Pierrot-Deseilligny, C. (1996). Location of the human posterior eye field with functional magnetic resonance imaging. *J Neurol Neurosurg Psychiatry, 60*(4), 445-448.

O'Driscoll, G. A., Alpert, N. M., Matthysse, S. W., Levy, D. L., Rauch, S. L., & Holzman, P. S. (1995). Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proc Natl Acad Sci U S A, 92*(3), 925-929.

O'Driscoll, G. A., Wolff, A. L., Benkelfat, C., Florencio, P. S., Lal, S., & Evans, A. C. (2000). Functional neuroanatomy of smooth pursuit and predictive saccades. *Neuroreport, 11*(6), 1335-1340.

Parker, A., & Gaffan, D. (1998). Memory after frontal/temporal disconnection in monkeys: conditional and non-conditional tasks, unilateral and bilateral frontal lesions. *Neuropsychologia, 36*(3), 259-271.

Parton, A., Nachev, P., Hodgson, T. L., Mort, D., Thomas, D., Ordidge, R., et al. (2007). Role of the human supplementary eye field in the control of saccadic eye movements. *Neuropsychologia, 45*(5), 997-1008.

Passingham, R. (1993). *The Frontal Lobes and Voluntary Action*. Oxford, UK: Oxford University Press.

Paus, T., Petrides, M., Evans, A. C., & Meyer, E. (1993). Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J Neurophysiol, 70*(2), 453-469.

Perlstein, W. M., Dixit, N. K., Carter, C. S., Noll, D. C., & Cohen, J. D. (2003). Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biol Psychiatry, 53*(1), 25-38.

Petrides, M. (1985). Deficits on conditional associative-learning tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia, 23*(5), 601-614.

Pierrot-Deseilligny, C., Milea, D., & Muri, R. M. (2004). Eye movement control by the cerebral cortex. *Curr Opin Neurol, 17*(1), 17-25.

Pierrot-Deseilligny, C., Muri, R. M., Nyffeler, T., & Milea, D. (2005). The role of the human

dorsolateral prefrontal cortex in ocular motor behavior. *Ann N Y Acad Sci, 1039*, 239-251.

Pierrot-Deseilligny, C., Muri, R. M., Ploner, C. J., Gaymard, B., Demeret, S., & Rivaud-Pechoux, S. (2003a). Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain, 126*(Pt 6), 1460-1473.

Pierrot-Deseilligny, C., Muri, R. M., Ploner, C. J., Gaymard, B., & Rivaud-Pechoux, S. (2003b). Cortical control of ocular saccades in humans: a model for motricity. *Prog Brain Res, 142*, 3-17.

Pierrot-Deseilligny, C., Ploner, C. J., Muri, R. M., Gaymard, B., & Rivaud-Pechoux, S. (2002). Effects of cortical lesions on saccadic: eye movements in humans. *Ann N Y Acad Sci, 956*, 216-229.

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., & Agid, Y. (1991). Cortical control of reflexive visually-guided saccades. *Brain, 114 (Pt 3)*, 1473-1485.

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., Muri, R., & Vermersch, A. I. (1995). Cortical control of saccades. *Ann Neurol, 37*(5), 557-567.

Ploner, C. J., Gaymard, B., Rivaud, S., Agid, Y., & Pierrot-Deseilligny, C. (1998). Temporal limits of spatial working memory in humans. *Eur J Neurosci, 10*(2), 794-797.

Ploner, C. J., Gaymard, B. M., Rivaud-Pechoux, S., Baulac, M., Clemenceau, S., Samson, S., et al. (2000). Lesions affecting the parahippocampal cortex yield spatial memory deficits in humans. *Cereb Cortex, 10*(12), 1211-1216.

Raemaekers, M., Jansma, J. M., Cahn, W., Van der Geest, J. N., van der Linden, J. A., Kahn, R. S., et al. (2002). Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. *Arch Gen Psychiatry, 59*(4), 313-320.

Raemaekers, M., Ramsey, N. F., Vink, M., van den Heuvel, M. P., & Kahn, R. S. (2006a). Brain activation during antisaccades in unaffected relatives of schizophrenic patients. *Biol Psychiatry, 59*(6), 530-535.

Raemaekers, M., Vink, M., van den Heuvel, M. P., Kahn, R. S., & Ramsey, N. F. (2006b). Effects of aging on BOLD fMRI during prosaccades and antisaccades. *J Cogn Neurosci, 18*(4), 594-603.

Ramnani, N., & Owen, A. M. (2004). Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. *Nat Rev Neurosci, 5*(3), 184-194.

Rivaud, S., Muri, R. M., Gaymard, B., Vermersch, A. I., & Pierrot-Deseilligny, C. (1994). Eye movement disorders after frontal eye field lesions in humans. *Exp Brain Res, 102*(1), 110-120.

Sakagami, M., & Niki, H. (1994a). Encoding of behavioral significance of visual stimuli by primate prefrontal neurons: relation to relevant task conditions. *Exp Brain Res, 97*(3), 423-436.

Sakagami, M., & Niki, H. (1994b). Spatial selectivity of go/no-go neurons in monkey prefrontal cortex. *Exp Brain Res, 100*(1), 165-169.

Sakagami, M., Tsutsui, K., Lauwereyns, J., Koizumi, M., Kobayashi, S., & Hikosaka, O. (2001). A code for behavioral inhibition on the basis of color, but not motion, in ventrolateral prefrontal cortex of macaque monkey. *J Neurosci, 21*(13), 4801-4808.

Sakai, K., & Passingham, R. E. (2003). Prefrontal interactions reflect future task operations. *Nat Neurosci, 6*(1), 75-81.

Sawaguchi, T. (1996). Functional modular organization of the primate prefrontal cortex for

representing working memory process. *Brain Res Cogn Brain Res, 5*(1-2), 157-163.
Schall, J. D. (2002). The neural selection and control of saccades by the frontal eye field. *Philos Trans R Soc Lond B Biol Sci, 357*(1424), 1073-1082.
Schall, J. D., Stuphorn, V., & Brown, J. W. (2002). Monitoring and control of action by the frontal lobes. *Neuron, 36*(2), 309-322.
Schiller, P. H., & Sandell, J. H. (1983). Interactions between visually and electrically elicited saccades before and after superior colliculus and frontal eye field ablations in the rhesus monkey. *Exp Brain Res, 49*(3), 381-392.
Schlag-Rey, M., Amador, N., Sanchez, H., & Schlag, J. (1997). Antisaccade performance predicted by neuronal activity in the supplementary eye field. *Nature, 390*(6658), 398-401.
Segraves, M. A., & Goldberg, M. E. (1987). Functional properties of corticotectal neurons in the monkey's frontal eye field. *J Neurophysiol, 58*(6), 1387-1419.
Shipp, S., Blanton, M., & Zeki, S. (1998). A visuo-somatomotor pathway through superior parietal cortex in the macaque monkey: cortical connections of areas V6 and V6A. *Eur J Neurosci, 10*(10), 3171-3193.
Simo, L. S., Krisky, C. M., & Sweeney, J. A. (2005). Functional neuroanatomy of anticipatory behavior: dissociation between sensory-driven and memory-driven systems. *Cereb Cortex, 15*(12), 1982-1991.
Simon, O., Mangin, J. F., Cohen, L., Le Bihan, D., & Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron, 33*(3), 475-487.
Sommer, M. A., & Wurtz, R. H. (2001). Frontal eye field sends delay activity related to movement, memory, and vision to the superior colliculus. *J Neurophysiol, 85*(4), 1673-1685.
Stuphorn, V., Taylor, T. L., & Schall, J. D. (2000). Performance monitoring by the supplementary eye field. *Nature, 408*(6814), 857-860.
Sweeney, J. A., Luna, B., Keedy, S. K., McDowell, J. E., & Clementz, B. A. (2007). fMRI studies of eye movement control: investigating the interaction of cognitive and sensorimotor brain systems. *Neuroimage, 36 Suppl 2*, T54-60.
Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R., et al. (1996). Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J Neurophysiol, 75*(1), 454-468.
Talairach, J., & Tournoux, P. (1988). *Co-Planar Stereotaxic Atlas of the Human Brain: A 3-Dimensional Proportional System, An Approach to Cerebral Imaging*. New York: Thieme Medical Publishers.
Tsujimoto, T., Ogawa, M., Nishikawa, S., Tsukada, H., Kakiuchi, T., & Sasaki, K. (1997). Activation of the prefrontal, occipital and parietal cortices during go/no-go discrimination tasks in the monkey as revealed by positron emission tomography. *Neurosci Lett, 224*(2), 111-114.
Tulving, E. (1983). *Elements of episodic memory*. Oxford [Oxfordshire] New York: Clarendon Press; Oxford University Press.
van Hooff, J. A. R. A. M. (1972). A comparative approach to the phylogeny of laughter and smiling. In R. A. Hinde (Ed.), *Nonverbal Communication* (pp. 209-241). Cambridge, UK: Cambridge University Press.
Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to

episodic memory retrieval. *Trends Cogn Sci, 9*(9), 445-453.
Ward, B. (2000). *Simultaneous Inference for fMRI Data*. In: AlphaSim program documentation for AFNI. Milwaukee: Medical College of Wisconsin.
Watanabe, M. (1986). Prefrontal unit activity during delayed conditional Go/No-Go discrimination in the monkey. II. Relation to Go and No-Go responses. *Brain Res, 382*(1), 15-27.
Wenban-Smith, M. G., & Findlay, J. M. (1991). Express saccades: is there a separate population in humans? *Exp Brain Res, 87*(1), 218-222.
White, I. M., & Wise, S. P. (1999). Rule-dependent neuronal activity in the prefrontal cortex. *Exp Brain Res, 126*(3), 315-335.