COGNITIVE CONTROL OF SIMPLE AND COMPLEX SACCADE TASKS IN VARYING CONTEXTS ASSESSED WITH FUNCTIONAL MRI

by

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(Under the Direction of Jennifer McDowell)

ABSTRACT

The context of a cognitive task influences an individual's ability to perform the task efficiently, with cognitive control adapting behavior to satisfy current goals. Saccade tasks provide an excellent model of cognitive control with simple prosaccades (rapid eye movements towards a stimulus) and complex antisaccades (movements to the mirror image location) representing lower and higher levels of cognitive control, respectively. In the first of three studies, saccades were presented in two mixed functional MRI tasks with either alternating blocks or randomly interleaved prosaccade and antisaccade trials. The second and third studies manipulated the cognitive demands of saccade tasks by presenting interleaved runs with a varying probability of antisaccade versus prosaccade trials (0, 25, 50, 75, or 100%) at baseline and post-test MRI sessions. Between the scans, participants practiced either the specific probability blocks used during testing or only a general 100% antisaccade block.

The results from the first study suggested that the more cognitively demanding interleaved context fostered transient responses in cognitive control circuitry for high conflict trials compared to sustained activation over single-trial-type blocks. Results from the second and third studies showed slower responses and fewer antisaccade errors in runs with a high

antisaccade probability. In the mixed probability runs, improbable performance of one trial type led to an augmented BOLD signal. Following practice, there was an overall reduction in BOLD signal within cognitive control and saccade circuitry, with the specific practice group showing additional regions with a strong signal decrease. These findings imply that with extended saccade practice the appropriate task set was selected in a more automatic manner with less top-down control, especially with exposure to mixed task contexts. Overall, cognitive control of behavior and brain activation supporting simple and complex saccade trial types is sensitive to the context in which the task is performed and more effort must be exerted to support a weak or unfamiliar task set.

INDEX WORDS: cognitive control; saccade; functional MRI; context; probability; task switching

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DEDICATION

For my grandmother

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Cognitive control is a broad term for a collection of supervisory mental processes, including attention, reasoning, inhibition, and working memory, that flexibly adapt behavior to current goals (Duncan & Owen, 2000; Miller & Cohen, 2001). Optimal responding in a given context relies upon knowledge about relevant stimuli and responses, integration of external cues with internal plans, and feedback on previous performance (Chatham et al., 2012; Meiran, 1996). The ability to control behavior based on prioritization of exogenous and endogenous signals allows for effortful decision-making and complex responses that extend beyond reflexive, immediate actions towards appetitive stimuli or away from aversive stimuli. Cognitive control operates across a number of cognitive domains, but one excellent model for quantifying these processes is the ocular motor system underlying saccade execution.

Saccades as a Model of Cognitive Control

A saccade is a rapid eye movement made to foveate a location of interest in the visual field. Two commonly studied saccade types are simple prosaccades (look towards a stimulus) and complex antisaccades (look towards the mirror image location of a stimulus; Hallett, 1978), which represent lower and higher levels of cognitive control demands, respectively. This differentiation arises because antisaccade trials require suppression of the prepotent tendency to look at a sudden stimulus onset, transformation of the stimulus location into the opposite visual field, and generation of an endogenous saccade (Hutton, 2008; McDowell, Dyckman, Austin, &

Clementz, 2008; Munoz & Everling, 2004). Prosaccades also engage cognitive mechanisms to a lesser degree, perhaps to identify the stimulus as a valid saccade target of interest, and prosaccade reaction times (RTs) are longer than neural transmission speeds require (Hutton, 2008). Antisaccade trials typically have slower RTs than prosaccade trials due to the added cognitive demands of making a volitional response and result in more directional errors (movements towards the stimulus which are interpreted as failures of cognitive control; Barton, Greenzang, Hefter, Edelman, & Manoach, 2006; McDowell et al., 2008; Noorani & Carpenter, 2013; Pierce, McCardel, & McDowell, 2015; Weiler & Heath, 2012). One benefit of using saccades as a model of cognitive control is the relatively simple nature of the stimuli and the motor response – almost any population can understand the basic instructions quickly and multiple features of the eye movements can be quantified precisely using modern infrared cameras or other eye tracking technology.

For both saccade trial types, data reveal RT variability within and between subjects for a single paradigm, and a number of computational models seek to explain this saccade behavior using neurophysiologically plausible systems. Carpenter and colleagues (Carpenter, 2000; Carpenter & Williams, 1995; Reddi & Carpenter, 2000) proposed the LATER (Linear Approach to Threshold with Ergodic Rate) model, which posits a baseline level of activity that rises towards a critical threshold for saccade generation. The rate of the linear rise changes randomly across trials with the accumulation of noisy neural input from multiple sources. This results in a different amount of time to reach the decision threshold on individual trials despite identical stimulus input and leads to a distributed range of saccade RTs. This fundamental concept also has been extended to models of saccade generation that involve a competition between simultaneous antisaccade and prosaccade task set activation (Cutsuridis, Smyrnis, Evdokimidis,

& Perantonis, 2007; Massen, 2004; Noorani & Carpenter, 2013; Trappenberg, Dorris, Munoz, & Klein, 2001). A task set is the collection of rules guiding the appropriate stimulus-response mapping that is associated with a given trial type (Rogers & Monsell, 1995; Vandierendonck, Liefooghe, & Verbruggen, 2010). Participants are given instructions as to what visual (or auditory) cues signify which trial type and must identify the cognitive or perceptual steps necessary to achieve the correct motor response. As described above, the prosaccade and antisaccade trial types rely upon a direct versus inverted sensory-motor transformation of the peripheral stimulus location, respectively; therefore, the prosaccade task set benefits from a strong visually-triggered response whereas the antisaccade task set must suppress this habitual response in order to execute the opposite motor command endogenously.

In saccade models, both task sets are initiated by the appearance of a peripheral stimulus, with top-down cognitive influences and bottom-up visual input biasing the time it takes each program to reach the motor threshold. The faster saccade program is the one ultimately executed (Massen, 2004). Often an antisaccade program is modeled as similar in form to a prosaccade program, but with a delay representing the sensorimotor inversion or volitional decision-making processes. Additionally, the base level of activity or rate of rise may differ between task sets (Dorris & Munoz, 1998; Noorani & Carpenter, 2013) or depending on instructional manipulations, trial history, or prior expectations (Reddi & Carpenter, 2000).

The current work addresses this last point – how the cognitive demands of a saccade task, especially the context in which it is performed, affect the competition between antisaccades and prosaccades. The context of a cognitive task may include factors such as the number of trials in the task, the types of trials performed together, the order of the trials, the setting in which the experiment is conducted, the time of day, what the participant had for breakfast, etc.

Modifications of behavior for each trial type under different contexts inform the understanding of how opposing task sets are maintained and selected in a changing environment. For example, generating antisaccades while completing a working memory task yielded more failures of suppression than performing antisaccade trials alone (Roberts, Hager, & Heron, 1994), as the tasks putatively made demands upon similar neural resources. Performing antisaccades and prosaccades in an interleaved task compared to blocks of a single trial type also resulted in more errors and slower RTs (Ethridge, Brahmbhatt, Gao, McDowell, & Clementz, 2009) because cognitive demands were increased as the opposing task sets competed for internal bias of motor commands. Repeated performance in a block strengthens a task set, while switching within a mixed context increases interference between trial types and prevents either task set from being fully engaged.

Neural Circuitry associated with Saccades

In addition to behavioral assessment, saccade tasks have been well studied with various neuroimaging techniques to characterize brain activation, including the blood oxygenation level dependent (BOLD) signal in functional magnetic resonance imaging (fMRI; Brown, Vilis, & Everling, 2007; Curtis & D'Esposito, 2003; DeSouza, Menon, & Everling, 2003; Ettinger et al., 2008; Ford, Goltz, Brown, & Everling, 2005; McDowell et al., 2008; Munoz & Everling, 2004). The BOLD signal indexes the concentration of deoxygenated hemoglobin in cerebral vasculature, which fluctuates as neural activity drives metabolic demand and increases local blood flow (Buxton, 2010; Logothetis & Wandell, 2004; Raichle & Mintun, 2006). This signal, therefore, serves as an indirect measure of brain activation that can be collected non-invasively with millimeter spatial resolution and temporal resolution on the order of seconds. Fundamental

regions of saccade circuitry observed with the BOLD signal (and electrophysiology) include occipital cortex, posterior parietal cortex (PPC), frontal and supplementary eye fields (FEF/SEF), basal ganglia, thalamus, cerebellum and superior colliculus (Brown, Goltz, Vilis, Ford, & Everling, 2006; Curtis & Connolly, 2008; Dyckman, Camchong, Clementz, & McDowell, 2007; Jamadar, Fielding, & Egan, 2013; Matsuda et al., 2004; Reuter, Kaufmann, Bender, Pinkpank, & Kathmann, 2010).

Saccade circuitry functions as a cooperative network during task performance, yet different regions are associated with specific processes. Once visual input is received on the retina and passed through the lateral geniculate nucleus of the thalamus, occipital cortex decodes information about the stimulus identity, while regions of the dorsal visual stream in PPC allocate spatial attention and perform visual-motor calculations (McDowell et al., 2008; Munoz & Everling, 2004). The intraparietal sulcus (IPS) within PPC is the putative human homolog of the parietal eye field identified in primate physiology studies that has connections to the brainstem and can trigger saccades directly (Gottlieb & Goldberg, 1999; Johnston & Everling, 2008; Krafft et al., 2012; Mort et al., 2003). FEF and SEF in frontal cortex possess both visual and motor saccade neurons, connect directly to the brainstem, and are related intimately to saccade generation and planning (Connolly, Goodale, Goltz, & Munoz, 2005; Everling & Munoz, 2000; Jamadar et al., 2013; Munoz & Everling, 2004; Schlag-Rey, Amador, Sanchez, & Schlag, 1997). The superior colliculus in the brainstem contains a retinotopic map of visual space with fixation neurons in the rostral pole and saccade neurons corresponding to increasingly larger amplitudes along a rostral-caudal axis (Dorris & Munoz, 1998; Krebs et al., 2010). When activity in one location in the superior colliculus map surpasses the motor threshold, projections to brainstem ocular motor nuclei ultimately initiate movements via the extraocular eye muscles (Munoz,

Dorris, Pare, & Everling, 2000). Together these widespread brain regions coordinate basic saccades that occur several times a second throughout the day.

Greater strength or extent of activation in this basic saccade circuitry and recruitment of additional regions including dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) occur when cognitive demands are high, such as during antisaccade trials (Amador, Schlag-Rey, & Schlag, 2004; Ettinger et al., 2008; Ford et al., 2005; Funahashi, 2014; McDowell et al., 2008; Munoz & Everling, 2004). DlPFC and ACC coordinate cognitive control processes in order to supervise and facilitate correct task behavior implemented by other regions of saccade circuitry (Badre & Wagner, 2004; Duncan, 2001; Duncan & Owen, 2000; Ettinger et al., 2008; Ford et al., 2005; Johnston, Levin, Koval, & Everling, 2007; Liston, Matalon, Hare, Davidson, & Casey, 2006; MacDonald, Cohen, Stenger, & Carter, 2000; Shenhav, Botvinick, & Cohen, 2013). These higher order association cortices have numerous feedback and feedforward loops with sensory and motor regions that allow a range of flexible behaviors within the nearly unlimited set of possible contexts for any task. PFC may be recruited proactively to support cognitive control in a sustained manner across trials when context predicts a high degree of conflict, or reactively to modulate cognitive control following an unexpected or transient task demand (Braver, 2012; Braver, Paxton, Locke, & Barch, 2009). Furthermore, the specific representations of PFC neurons may adapt according to the task at hand so that a finite number of cells can support the acquisition of myriad task sets (Duncan, 2001; Freedman, Riesenhuber, Poggio, & Miller, 2001). Yet the complex flexibility of lateral PFC is not without organization: there is a proposed continuum from anterior to posterior regions that shifts from abstract task representations towards concrete, temporally-relevant task information (Badre, 2008; Christoff & Gabrieli, 2000; Koechlin & Summerfield, 2007). Despite the advancements that have been made

in characterizing PFC's multi-faceted involvement in cognitive control, many questions remain and the current studies seek to further elucidate the impact of context on PFC control of saccade tasks.

In order to receive and integrate cognitive control signals, lateral PFC relies upon strong functional and structural connections to medial PFC and cingulate cortex (Blumenfeld, Nomura, Gratton, & D'Esposito, 2013; Duncan, 2001). The ACC has been identified in not only antisaccade tasks, but also in a range of cognitive paradigms. Current theories attribute its primary function in cognitive control as conflict monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter & van Veen, 2007; Liston et al., 2006). When multiple task sets are activated simultaneously, stimuli are perceptually ambiguous, or recent behavior conflicts with goal pursuit, the ACC is activated to signal the necessity for stronger top-down control to resolve such conflict and select an appropriate response. For the present work, the BOLD signal in both ACC and PFC in various contexts is of particular interest as a means of assessing how cognitive control is recruited by conflict-monitoring systems and engaged to satisfy changing task demands.

The Role of Context in Cognitive Control of Saccade Generation

The current set of studies investigates the role of context in shaping saccade behavior and brain activation using BOLD fMRI in paradigms that manipulate trial structure and trial type probability, and examines the effects of extended practice on improving these measures. In Chapter 2, the first study focuses on differences due to trial structure and task switching by comparing blocked and interleaved mixed saccade tasks. The blocked task alternates between repeated, predictable presentation of each trial type, while the interleaved task presents the two

trial types randomly. In Chapter 3, the second study looks more closely at the interleaved context, presenting participants with three mixed tasks of varying probability of an antisaccade trial versus a prosaccade trial. This study investigates how infrequent performance of one trial type or the other creates a context that may bias task set competition and engage cognitive control beyond normal task demands. Finally in Chapter 4, the third study looks at how daily practice of saccade tasks changes these initial trial type probability response patterns in two practice groups. General practice of only the complex antisaccade trials may yield improvements in behavior and reductions in activation, or specific practice of the trial type probability context may be necessary for participants to learn effective response strategies and strengthen task sets.

As task demands increase through conflicting trial history or low trial type probability, eye movement behavior is predicted to slow and result in more directional errors. Accordingly, cognitive control processes will be engaged to modulate visual input and task set representations in the saccade network. Cognitive control regions including ACC, dlPFC, and PPC are expected to play a central role in mediating top-down effects of context on saccade circuitry and behavioral outcomes. With practice, the behavioral costs of high-conflict contexts should diminish and brain activation should be reduced as less cognitive effort is exerted. Together these studies will demonstrate how a changing context differentially recruits cognitive control and how immediate trial history and extended task practice modify the brain's execution of a cognitive task.

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CHAPTER 2

THE ROLE OF ANTERIOR CINGULATE CORTEX IN COGNITIVE CONTROL OF SACCADE TASK CONTEXT AND SWITCHING[1]

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Abstract

The context of a cognitive task influences one's ability to successfully perform the task, with cognitive control mechanisms flexibly adapting behavior to meet current goals. Mixing multiple trial types in a single task results in increased cognitive demands on working memory maintenance and task switching processes, supported by stronger brain activation in a frontal-parietal-cingulate cognitive control network. Saccade tasks provide an excellent model of cognitive control with prosaccades (rapid eye movements towards a stimulus) and antisaccades (movements to the mirror image location of a stimulus) representing low and high levels of cognitive control, respectively. In order to determine how cognitive control is differentially recruited according to contextual biases on task set activation and switching, saccades were presented in two mixed functional MRI tasks with either alternating blocks of prosaccade and antisaccade trials or randomly interleaved presentation of both trial types. Results indicated that the interleaved context led to slower prosaccade responses, more antisaccade errors, and increased BOLD signal in cognitive control circuitry during antisaccades and switch trials. The blocked context resulted in better behavioral performance and similar activation for both saccade trial types in these regions. Critically, the ACC demonstrated a strong, transient BOLD signal only during antisaccade switch trials in the interleaved context when both the inherent task set instructions and contextual trial history necessitated effortful supervision of task selection for these high conflict trials. Task switching processes, therefore, likely draw upon similar cognitive control resources as novel task set performance to facilitate appropriate stimulus-response mapping based on context.

Introduction

The context in which a task is performed influences response efficiency based on recent experience with particular stimuli or task rules. The contextual factors of paradigm design and trial history impact behavior on laboratory tasks: when participants perform a single trial type repeatedly or alternate between two trial types, responses reflect the additional cognitive costs of maintaining multiple trial types in working memory and switching between task rules/sets between trials (Kiesel et al., 2010; Meiran, 1996; Rogers & Monsell, 1995; Vandierendonck, Liefooghe, & Verbruggen, 2010; Wylie, Javitt, & Foxe, 2003). A task set is the collection of perceptual, cognitive, and motor processes necessary to perform the instructed response following a certain stimulus (Rogers & Monsell, 1995). Cognitive control is a set of supervisory processes that shape context-dependent performance by identifying immediately relevant goals and facilitating the appropriate task set and stimulus-response pairing. Across cognitive domains, brain activation is observed in frontal, parietal, and anterior cingulate cortical regions during cognitive control paradigms, as well as in task-specific circuitry (Badre, 2008; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Hutton, 2008; Miller & Cohen, 2001).

One model for investigating cognitive control is the ocular motor system underlying saccade production – a basic prosaccade (rapid eye movement towards a newly appearing peripheral stimulus) contrasts with a complex antisaccade (a movement away from the stimulus to the mirror image location). Unlike many task switching paradigms, both saccade trial types use the same stimulus and require a similar motor response with only the instructed direction of response changing. Antisaccades necessitate the recruitment of greater cognitive control to suppress a prepotent response towards the target, invert the visual-motor spatial vector, and volitionally generate a saccade to an unmarked location (Hutton, 2008; McDowell, Dyckman,

Austin, & Clementz, 2008; Munoz & Everling, 2004). Saccade tasks have been thoroughly studied in previous literature and antisaccade trials typically result in more directional errors, slower correct reaction times (RTs), and stronger blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) signal in saccade brain circuitry than during prosaccade trials (Brown, Vilis, & Everling, 2007; Curtis & D'Esposito, 2003; DeSouza, Menon, & Everling, 2003; Ettinger et al., 2008; Ford, Goltz, Brown, & Everling, 2005; McDowell et al., 2008; Munoz & Everling, 2004; Noorani & Carpenter, 2013; Pierce, McCardel, & McDowell, 2015; Weiler & Heath, 2012).

Previous studies that presented saccade tasks in different contexts reported both behavioral effects and BOLD signal changes. Ethridge and colleagues (2009) compared behavior on prosaccade and antisaccade trials using separately blocked or randomly interleaved presentations. They found that in the separate condition saccade responses were faster and yielded fewer errors than in the interleaved conditions (Ethridge, Brahmbhatt, Gao, McDowell, & Clementz, 2009), because the context of separate trial performance facilitated the active task set while the interleaved context required frequent switching of task sets leading to a weaker task representation. In Dyckman et al. (2007), participants performed saccades in two different contexts in the fMRI environment: single task (blocks of only prosaccade or antisaccade trials versus fixation) or mixed tasks (alternation between blocks of prosaccade and antisaccade trials). The single context showed significantly greater activation for antisaccades compared with prosaccades in typical saccade circuitry including cuneus, posterior parietal cortex (PPC), and frontal and supplementary eye fields (FEF/SEF; for reviews of saccade circuitry see Jamadar, Fielding, & Egan, 2013; McDowell et al., 2008), as well as in prefrontal cortex (PFC). The mixed context, however, only resulted in antisaccade-specific increases in the FEF, SEF and

precuneus, suggesting that activation in other regions such as PFC was sustained across both tasks in order to maintain and switch between the two task sets (Dyckman, Camchong, Clementz, & McDowell, 2007). Unfortunately, the mixed task condition in that study did not include a fixation baseline, which prohibited quantification of the saccade-related activation except as a relative measure between prosaccade and antisaccade trials. The current study utilized a blocked design that alternated between fixation, prosaccade, and antisaccade blocks to clarify the role of PFC and other control regions during sustained, mixed task set activation.

Another pair of studies specifically evaluating trial history effects on interleaved saccade tasks (Lee, Hamalainen, Dyckman, Barton, & Manoach, 2011; Manoach et al., 2007) found differential activation in FEF and SEF following a previous antisaccade trial, as well as transient signal changes in FEF and anterior cingulate cortex (ACC) following a task switch. The ACC generally is engaged to detect trial conflict and upregulate other cognitive control regions to enhance the likelihood of successful behavior (Botvinick et al., 2001; Braver, Barch, Gray, Molfese, & Snyder, 2001; Ford et al., 2005; Nee, Kastner, & Brown, 2011). Task switching studies using alternate behavioral paradigms (Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Kimberg, Aguirre, & D'Esposito, 2000; Muhle-Karbe, De Baene, & Brass, 2014; Smith, Taylor, Brammer, & Rubia, 2004; Sylvester et al., 2003; Yeung, Nystrom, Aronson, & Cohen, 2006) reported greater activation on switched trials relative to repeated trials in regions including ACC, dorsolateral PFC, and PPC. This activation may support a general cognitive control or attention network during switching, yet some findings indicated that these effects were not due to active task switching *per se* but to maintenance of, or competition among, multiple task sets (Brass & von Cramon, 2002; Gruber, Karch, Schlueter, Falkai, & Goschke, 2006; Ruge, Jamadar, Zimmermann, & Karayanidis, 2013). The use of mixed saccade trials in the present

study may provide insight into this debate by investigating not only how task switch and repetition trials differ, but also how these factors interact with asymmetric task sets (Cherkasova, Manoach, Intriligator, & Barton, 2002). The simple prosaccade trial type constitutes a habitual, stimulus-driven response, but the antisaccade trial type stands in direct competition with this potent tendency. Therefore, additional activation increases for antisaccade task switch trials could demonstrate the engagement of control processes beyond that required for the inherent task set competition involved in a repeated antisaccade.

In the current study, we presented participants with mixed saccade trials in two task contexts. One task consisted of repeating blocks of prosaccades, antisaccades, and fixation; the second task consisted of pseudo-randomly interleaved prosaccade and antisaccade trials with varying inter-trial fixations. Both contexts putatively made moderate demands upon working memory because both trial type task sets had to be maintained throughout both task contexts, though perhaps to a different extent. The blocked task, however, had a consistent, predictable trial order with the same trial type performed multiple times consecutively, whereas the interleaved task had an unpredictable trial order involving numerous task switches. It was hypothesized that the blocked context would be the easiest for participants due to the repeated performance of a series of each trial type, resulting in fewer errors, faster RTs, and weaker BOLD signal in both saccade circuitry and cognitive control regions than the interleaved context. Because task switching within the interleaved task was predicted to contribute strongly to these differences, switched trials were expected to be associated with more errors, slower RTs, and stronger BOLD signal than repeated trials. The interactions between trial type and task context or switching should reveal how trial history influences cognitive control of a habitual or novel task set and how the brain detects and responds to contextual conflict for simple and complex tasks.

Methods

Participants

Data are reported from 30 right-handed, healthy participants (mean age = 19.5 years, SD = 3.7; 10 males), who experienced no current major psychiatric disorders or substance abuse, had no metal implants, and had normal or corrected-to-normal vision (via self-report), as described previously (Pierce & McDowell, 2016b) with 5 individuals excluded from the current analyses due to low trial numbers (fewer than 3 valid trials in at least one task switching category). All participants provided written informed consent and activities were approved by the Institutional Review Board of the University of Georgia.

Task Design

Participants completed saccade trials in two task contexts: one blocked task and one interleaved, rapid event-related task. The blocked task consisted of 20-second blocks of fixation, 10 prosaccade trials, and 10 antisaccade trials presented in alternating order (FPFA) with four blocks of each trial type and nine blocks of fixation. The interleaved task consisted of 30 prosaccade and 30 antisaccade trials presented in pseudo-random order with jittered fixation periods. All stimuli consisted of a 1° gray shape presented on a black background (Pierce & McDowell, 2016b). During fixation a cross appeared in the center of the screen: for the blocked task the fixation within the saccade blocks lasted for 500 ms before each trial; for the interleaved task the fixation lasted for 2000 to 8000 ms (average 3500 ms) between trials. For saccade trials in both tasks, the trial type cue was illuminated around the cross for 500 ms (for prosaccades, a square; for antisaccades, a diamond). This was followed by a blank screen for 200 ms ("gap" presentation) and finally the peripheral stimulus at 5° or 10° right or left of the center for 800 ms. Two peripheral stimulus eccentricities were included to reduce the likelihood of participants'

anticipating the response location and preparing a motor response in advance (data collapsed across amplitude for analyses).

Procedure

Participants attended an initial screening session, where they completed demographic surveys and were screened for exclusion criteria. Participants were introduced to the saccade task with twenty practice trials of mixed prosaccades (look as quickly and accurately as possible towards the peripheral stimulus) and antisaccades (look to the opposite location of the stimulus, same distance from the center). During the subsequent MRI session, a high-resolution structural scan was obtained first for each participant, followed by several event-related functional scans (only one of which is reported here), and the blocked task scan. Participants were not given any information beforehand about the different task contexts they would perform, but simply were told to complete the appropriate response as indicated by the square or diamond trial type cue on each trial. Stimuli were displayed using Presentation software (Neurobehavioral Systems, Albany, CA) and a dual mirror system attached to the head coil that allowed a participant to view a projection screen at his/her feet and researchers to monitor the participant's eye. Right eye pupil position was sampled at 60 Hz (IView X MRI-LR system, SensoMotoric Instruments, Germany) and recorded for off-line analysis. Before beginning the saccade tasks, eye position was calibrated using IView's 5-point calibration and an in-house horizontal calibration.

Imaging Parameters

MR images were collected on a 3T GE Signa Excite HDx system (General Electric Medical Systems, Milwaukee, WI) at the University of Georgia Bio-Imaging Research Center. A high-resolution anatomical image was collected using a T1-weighted 3D FSPGR sequence (echo time (TE) = 3 ms, flip angle = 20°, field of view (FOV) = 240 mm x 240 mm, matrix size 256 x

256, 150 axial slices, in-slice resolution = 0.94 x 0.94 mm, slice thickness = 1.2 mm, scan time=6:32). The functional scans were collected using a T2*-weighted gradient echo EPI sequence (TE = 30 ms, repetition time (TR) = 2000 ms, flip angle = 90°, FOV =220 mm x 220 mm, matrix size = 64 x 64, 33 interleaved oblique slices aligned with the AC-PC plane, in-slice resolution = 3.4 x 3.4 mm, slice thickness = 4 mm, and 4 dummy volumes for magnet stabilization). The event-related scan had 158 volumes with a scan time of 5 minutes 24 seconds, and the blocked scan had 170 volumes with a scan time of 5 minutes 48 seconds.

Analyses

Eye position data were analyzed using custom scripts written in MATLAB (MathWorks, Natick, MA). Trials were manually scored for initial direction of response (eye movements with velocities surpassing 20°/sec were classified as saccades) and reaction time (RT). Error rate was defined as the number of trials with an initial saccade in the incorrect direction divided by the total number of scoreable trials; RT was defined as the time from the appearance of the peripheral circle to the initiation of the first saccade. Trials with no response, blinks at stimulus onset, anticipatory saccades (faster than 90 ms RT or during the gap window), or with insufficient data quality due to loss of pupil tracking were excluded from further analyses. Based on these criteria, an average of 73 of 80 trials per participant from the blocked task and 54 of 60 trials from the interleaved task were included in the initial analysis. A 2x2 (context (blocked/interleaved) by trial type (anti/pro)) ANOVA was performed to compare error rates and RTs for correct trials for both trial types between the task contexts.

To further characterize responses within the interleaved task, trials were sorted based on current and previous trial type (Cherkasova et al., 2002; Chiau et al., 2011; Manoach et al., 2007): prosaccade following a prosaccade (repeated prosaccade), prosaccade following an

antisaccade (switched prosaccade), antisaccade following an antisaccade (repeated antisaccade), and antisaccade following a prosaccade (switched antisaccade). A 2x2 (task switch (repeated/switched) by trial type (anti/pro)) ANOVA was performed to compare error rates and RTs for correct trials. For the RT (and BOLD signal) analysis, only trials on which the participant made a directionally correct response on the current and previous trial were included (average of 40 per participant) to describe most accurately a successful task switch while minimizing effects due to differences in error rate. Statistical analyses on eye movement metrics were performed using SAS Version 5.1 (SAS Institute Inc., Cary, NC) and SPSS Version 22 (IBM Corp., Armonk, NY) software packages.

Functional MRI data were analyzed using the AFNI software package (Cox, 1996, 2012) with initial processing steps including: slice-timing correction, volume alignment, resampling to 4 mm^3 voxel grid, spatial standardization to a Talairach template, spatial smoothing (4 mm full width-half maximum Gaussian kernel), and voxel-wise scaling to a mean of 100. For the comparison between the blocked and interleaved tasks, individual subject data for each task were submitted to a general linear model with stimulus regressors for prosaccade and antisaccade trials, as well as regressors of no interest to remove effects from baseline drift (linear, quadratic, cubic) and rotational movement in the x, y, and z planes. Voxel-wise model coefficients then were entered into a 2x2 (task context (blocked/interleaved) by saccade trial type (anti/pro)) repeated measures ANOVA. Trial type main effects from the same participants have been reported previously (Pierce & McDowell, 2016b) and are omitted here.

For the task switching analysis within the interleaved task, a general linear model was fit based on each participant's behavioral responses with stimulus regressors for repeated prosaccades, switched prosaccades, repeated antisaccades, and switched antisaccades for trials

with a correct response on the current and previous trial. Regressors of no interest also were included for error responses and unscored trials, baseline drift (linear, quadratic, cubic) and rotational movement in the x, y, and z planes. Coefficients for correct trials then were entered into a 2x2 (task switch (repeated/switched) by trial type (anti/pro)) repeated measures ANOVA.

To limit statistical comparisons and focus on regions of potential neural activity, the group analyses were confined to regions within a custom brain mask created from the average gray matter segmentation from all subjects' anatomical images using FSL's FAST (FMRIB Software Libraries Automated Segmentation Tool; Zhang, Brady, & Smith, 2001) in conjunction with putamen, caudate, and thalamus regions as defined by AFNI's Talairach-Tournoux atlas (Talairach & Tournoux, 1988). To protect against false positives resulting from multiple comparisons across voxels, a clustering method derived from Monte Carlo simulations was applied to the group maps to determine the minimum cluster size needed for statistical significance while accounting for the shared spatial information in the data (AFNI's 3dclustsim). With an initial voxel-wise threshold of $p<.025$, a family-wise $\alpha<.05$ was preserved by clusters with a minimum of 42 voxels.

Finally, to determine whether any regions differentiated both task context and task switching according to trial type, a conjunction map was constructed using the clusters identified in each interaction effect (bottom panels of Figs. 2.2 and 2.4). A binary map of the task context by trial type interaction was generated with significant voxels having a value of 1 and non-significant voxels having a value of 0. This map was then overlaid on a similar binary map of the task switching by trial type interaction so that voxels common to both interactions had a value of 2 in the final conjunction map. The average BOLD signal change then was extracted from the shared voxels for each trial condition within the interleaved and blocked contexts.

Results

Blocked vs. Interleaved Behavioral Responses

The task context by trial type ANOVA showed a main effect of trial type with typical antisaccade costs for both error rate ($F(1,29)=108.0$, $p<.01$, $\eta^2=.79$) and RT ($F(1,29)=223.1$, $p<.01$, $\eta^2=.89$). There was also a main effect of context on error rate ($F(1,29)=20.7$, $p<.05$, $\eta^2=.42$) with more errors in the interleaved context, but no effect on RT ($F(1,29)<1$, p=n.s.). The error rate effect was driven by a significant interaction ($F(1,29)=7.1$, $p<.05$, $\eta^2=.20$) between trial type and context, showing that antisaccade trials in the interleaved task context (M=24.4%, SD=11.1) yielded more errors than in the blocked task (M=16.1%, SD=10.9). There was also an interaction effect for RT ($F(1,29)=6.0$, $p<.05$, $\eta^2=.17$), showing that prosaccade trials in the interleaved task context (M=201 ms, SD=27) resulted in slower correct RTs than in the blocked task (M=193 ms, SD=21), as shown in the left panels of Figure 2.1.

Interleaved Task Switching Behavioral Responses

The task switching ANOVA for the interleaved task showed a main effect of trial type with antisaccade trials yielding more errors ($F(1,29)=93.5$, $p<.01$, $\eta^2=.77$) and slower RTs ($F(1,29)=118.3$, $p<.01$, $\eta^2=.80$), than prosaccade trials. There was also a main effect of task switching for error rate ($F(1,29)=16.4$, $p<.01$, $\eta^2=.36$) and correct RT ($F(1,29)=14.7$, $p<.01$, $\eta^2=.34$) with more errors and slower RTs in the task switching condition. The interaction effect ($F(1,29)=22.0$, $p<.01$, $\eta^2=.43$) demonstrated that switched antisaccade trials (M=30.7%, SD=14.3) yielded more errors than repeated antisaccade trials (M=17.1%, SD=13.0) and switched prosaccade trials (M=207 ms, SD=31) resulted in marginally slower correct RTs ($F(1,29)=3.4$, $p=.08$, $\eta^2=.11$) than repeated prosaccade trials (M=194 ms, SD=26), as shown in the right panels of Figure 2.1. Additionally, neither trial type's repeated error rate (anti: $t(29)<1$,

p=n.s.; pro: *t*(29)=1.79, *p*=n.s.) or RT (anti: *t*(29)=1.32, *p*=n.s.; pro: *t*(29)<1, *p*=n.s.) differed from the blocked context.

Blocked vs. Interleaved BOLD Signal Changes

The ANOVA comparing BOLD signal in the blocked versus interleaved task context revealed main effects of task context in eight significant clusters including: left parietal cortex (postcentral gyrus and inferior parietal lobule), left anterior cingulate, left superior/middle frontal gyrus (SFG/MFG), bilateral insula, bilateral cuneus, right culmen in the cerebellum, and right MFG/inferior frontal gyrus (IFG; Table 2.1). Figure 2.2 (top) displays a map of the *t*-test between task contexts, indicating that the interleaved context showed greater BOLD signal in seven of the eight clusters including visual processing and cognitive control regions (orange). Right MFG was the only region that showed greater BOLD signal for the blocked task (blue).

The task context by saccade trial type interaction resulted in eight significant clusters including: right precuneus, right MFG/IFG, right cingulate/SFG, left middle occipital gyrus (MOG)/cuneus, bilateral caudate, left lingual gyrus, and right temporal cortex (Table 2.1). Figure 2.2 (bottom) displays the brain map of *F*-values for the interaction, with stronger effects shown in brighter colors. Figure 2.3 shows the average BOLD signal from three regions representing the three observed patterns of results: the right precuneus region (as well as right temporal and left occipital cortex) had positive BOLD signal for all trial conditions, but with greater signal for antisaccade trials in the interleaved task. The right cingulate/SFG region (and bilateral caudate) had positive BOLD signal only for the antisaccade interleaved trials. Finally, the right MFG alone showed positive BOLD signal for all conditions except the prosaccade trials in the interleaved task, which had no signal change from baseline. Overall the blocked context had

more similar activation levels for antisaccade and prosaccade trials, while the interleaved context showed an increase specific to antisaccade trials.

Interleaved Task Switching BOLD Activation

The ANOVA comparing BOLD signal for task switching conditions within the interleaved context yielded four significant clusters for the switching main effect: right precuneus, right inferior parietal lobule (IPL), bilateral cingulate, and right middle occipital gyrus (MOG; Figure 2.4/Table 2.2). All of these regions showed greater BOLD signal during task switch trials; no regions showed greater signal during repeated trials. The interaction effect between task switching and saccade trial type yielded three significant clusters (Figure 2.4/Table 2.2), including left IPL, bilateral cingulate and thalamus. Cingulate and thalamus showed the strongest BOLD signal for switched antisaccade trials, while the left IPL cluster showed positive BOLD signal for all trials except repeated prosaccades (Figure 2.5).

The conjunction map of the significant clusters from the interaction effects for both task context by saccade trial type, and task switching by trial type revealed a single region encompassing the ACC. This region exhibited a strong positive BOLD signal only during antisaccade switched trials in the interleaved task context (Figure 2.6/Table 2.2). Prosaccade trials and the blocked context showed no significant signal change in this region.

Discussion

In this study, the behavioral and neural correlates of context-dependent performance were examined using saccade tasks. Participants completed prosaccade and antisaccade trials in two task contexts – one context presented trials in repeating blocks of single trial types while the other context presented trials in a randomly interleaved manner. The interleaved context resulted

in more antisaccade errors and slower prosaccade RTs than the blocked context, and elicited a stronger BOLD signal in widespread visual, motor, and cognitive control brain regions, especially during antisaccade trials. Within the interleaved task, the effects of switching task sets from the previous trial also were investigated. The behavioral costs in the interleaved task were restricted to task switch trials, which resulted in stronger BOLD signal in ACC, PFC, and PPC. The ACC, in particular, was involved in all context comparisons, showing a strong BOLD signal only for antisaccade switch trials in the interleaved task. This region supports cognitive control and conflict monitoring processes and the observed augmentation of BOLD signal when switching to an antisaccade trial indicates greater top-down control during this specific trial configuration. Switching to a novel task set following a simple but dominant response, therefore, made particular demands for cognitive control of task set selection and reconfiguration in an interleaved compared to a blocked context.

Behavioral Responses

Analyses of the behavioral response patterns across contexts revealed that error rates were higher for antisaccade trials in the interleaved context than in the blocked context. Interestingly, this increase was confined to switched trials within the interleaved context, suggesting that there were no additional working memory demands overall that made repeated trials differ from the blocked context where most trials were repetitions of the same trial type. The higher error rate on switched antisaccade trials demonstrated that when a participant had to activate the antisaccade task set after performing a prosaccade trial, he/she was less likely to suppress a saccade towards the peripheral stimulus as required because the prosaccade task set remained active and created interference. The opposite pattern was not observed as prosaccade

error rates were low across conditions, indicating that this habitual, stimulus-driven response was performed correctly in spite of any antisaccade interference.

Prosaccade RTs were impacted by a previous antisaccade trial, however, and were slowed for switched trials within the interleaved context. This is consistent with studies that found a unilateral effect of switching, with no differences in antisaccade RTs (Chan & DeSouza, 2013; Pierce & McDowell, 2016a; Weiler & Heath, 2012, 2014), although other studies found slower responses for both trial types following an antisaccade trial (Barton, Greenzang, Hefter, Edelman, & Manoach, 2006; Cherkasova et al., 2002; Lee et al., 2011; Manoach et al., 2007; Pierce et al., 2015). It therefore remains an open question whether RT effects result from task switching reconfiguration or lingering suppression from a previous antisaccade, although both factors likely interact in selecting the appropriate task set and depend on experimental parameters in the context of each study.

Task Context and Switching BOLD Effects

The effects of task context and switching were investigated via the BOLD fMRI signal associated with each saccade trial condition. Overall, the interleaved context showed stronger activation than the blocked context, and switched trials within the interleaved context showed stronger activation than repeated trials. The activation increases in the interleaved context were specific to the difficult antisaccade and/or task switch trials, suggesting a temporally transient control mechanism that did not remain engaged for less conflicting prosaccade or task repeat trials. In contrast, the blocked context results showed sustained task engagement with similar BOLD signal for both trial types in the identified cognitive control regions. Although fMRI designs for blocked and interleaved contexts necessarily differ and blocked designs traditionally

produce greater signal to noise ratio (by accumulating activation over multiple trials), the results showed generally comparable percent signal change for both designs.

Cognitive control circuitry including ACC, PFC, and PPC showed stronger BOLD signal for antisaccades and switched trials, consistent with previous reports (Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005; Braver, Reynolds, & Donaldson, 2003; Brown et al., 2007; Dreher, Koechlin, Ali, & Grafman, 2002; Hakun & Ravizza, 2012; Jamadar et al., 2013; McDowell et al., 2008; Ravizza & Carter, 2008). The use of saccade tasks in this study, however, allowed for comparison of nearly identical trial conditions where only the task rule corresponding to a particular stimulus-response mapping differed from one trial type to the other. The inherent asymmetry between the dominant prosaccade response and the complex antisaccade response provided a means of comparing task set switching and reconfiguration for habitual and novel behaviors. Each of the context and switching comparisons identified differential activation in the ACC, a region critical to cognitive control monitoring. In medial frontal cortex regions extending from rostral ACC to the pre-supplementary motor area showed more BOLD signal for the interleaved context and antisaccade trials. The conjunction map between the two interaction effects' clusters identified only the ACC as common to both comparisons. This region was primarily sensitive to the demands of antisaccade task switching trials – an instance where the intrinsic stimulus-response mapping reversal and previous trial history converged to created high conflict for task selection processes. Neither repeated antisaccades nor switched prosaccades showed the same signal increase in this conjunction region, indicating that the ACC responded to the combined demands of task switching and task set competition in a manner distinct from a simple additive effect of each demand occurring separately. As only correct trials were analyzed for the task switching comparison, the

heightened BOLD signal in ACC for antisaccade switch trials evidently supported effective task selection in frontal cortex and facilitation of the appropriate task set in parietal and occipital cortex (Liston, Matalon, Hare, Davidson, & Casey, 2006; Miller & Cohen, 2001), although the commission of errors on earlier trials of this type may have recruited activation subsequently to ensure correct performance.

In prefrontal cortex, right MFG showed greater BOLD signal during the blocked context, as well as an interaction with trial type, due to a weak signal during prosaccade trials in the interleaved context. The blocked context may have resulted in stronger BOLD signal in this region due to sustained activation of task selection and attention processes across saccade blocks compared to disengagement during fixation blocks. In the interleaved context, right MFG may have been engaged only during antisaccade trials in a transient manner to facilitate the unfamiliar stimulus-response mapping, while the longer, irregular fixation intervals between trials allowed control to be disengaged for low demand prosaccade trials. Left anterior PFC (SFG/MFG), on the other hand, showed greater overall BOLD signal in the interleaved context, perhaps reflecting repeated efforts at overcoming interference by the recently activated opposing task set that did not decay sufficiently between trials (Kiesel et al., 2010).

The increased activation in frontal control regions was mirrored by posterior parietal cortex. Regions including precuneus and IPL showed increased BOLD signal for highly demanding antisaccade and switch trials in the interleaved context, consistent with increased task demands that necessitated greater involvement of parietal visuospatial attention, potentially in relation to the large number of errors committed for this trial type overall. Left IPL, in particular, showed moderate BOLD signal in the interleaved context for all conditions except repeated prosaccades, arguably the easiest response for participants to generate. As with the reduced

signal for prosaccades overall in the interleaved context in right MFG, this response pattern suggests that control mechanisms were engaged transiently in the interleaved context for high conflict trials and released during trials requiring a habitual or recently performed response. The blocked context, in contrast, showed similar activation in PPC for both trial types. The interleaved context with random trial timing was more conducive to eliciting and detecting such transient responses restricted to high conflict trials, while the rapid pacing of the blocked saccade trials perhaps encouraged participants to maintain an active task set representation throughout blocks of either trial type. Here again, the saccade paradigm provided an advantage over other task switching studies by providing an additional dimension for comparison (habitual/novel response) while still relying on the same stimulus input (peripheral circle) and fundamental motor output. Differences in these control regions therefore can be related more directly to switching of task rules rather than perceptual processing or cognitive domain.

In addition to supervisory cognitive control regions, extensive portions of visual cortex showed greater BOLD signal in the interleaved context, with a moderate signal change observed for the blocked context. Antisaccades and switched trials in the interleaved context yielded stronger BOLD signal in cuneus, lingual gyrus, MOG, and posterior temporal cortex compared to the blocked context and prosaccade trials. This activation likely reflected increased attentional demands on selecting the stimulus-response mapping corresponding to the current trial type cue shape. The random trial presentation in the interleaved context frequently resulted in a change in visual stimulus (trial type cue) for switch trials, while in the blocked context the visual stimulus was the same across the block of trials and therefore elicited a weaker, adaptive response from the visual system.

The context and switching comparisons also identified several other regions that typically yield greater activation for antisaccade over prosaccade trials, including insula, thalamus, caudate, and cerebellum (Brown, Goltz, Vilis, Ford, & Everling, 2006; Dyckman et al., 2007; Krafft et al., 2012; van Broekhoven et al., 2009). This activation reflects the increased cognitive demands of a complex saccade task, and here bilateral insula and right culmen (cerebellum) showed a stronger BOLD signal in the interleaved context. The caudate and thalamus had greater signal for (switched) antisaccades in the interleaved context, when additional control often was needed to select the correct task set corresponding to the visual trial type cue. Differential activation in these regions indicates that contextual effects on saccade trials are distributed throughout the circuitry, perhaps in response to changes in higher order cognitive control regions such as PFC and ACC.

A previous study of trial history in saccade tasks (Manoach et al., 2007) reported reduced BOLD signal in FEF and SEF following a previous antisaccade trial. While clusters in the present results may have extended partially into regions consistent with FEF/SEF, it is uncertain that this reflected true saccade-related neuron activity. Manoach and colleagues (2007) focused on the earliest segments of the BOLD response (0-4 seconds) that may have been driven primarily by preparatory activity, while the current analyses encompassed both trial type cue and saccade generation processes. As such, the FEF/SEF may have shown stronger differences following an antisaccade early in the trial, while the motor component of the response was more similar across conditions, and thus was not detected by the present comparisons (although there was no RT effect of a previous antisaccade on current antisaccade trials either). The current study, however, included a relatively low number of each task switching trial type, which may have weakened the reliability of the BOLD signal estimates.

Conclusions

In this study, the effects of task context and switching were investigated in mixed saccade paradigms using behavior and BOLD fMRI. Frequent switching of trial types in the interleaved task context led to behavioral costs coupled with increased brain activation in cognitive control and task-specific circuitry distinct from overall maintenance of multiple task sets required in a mixed block design that resulted in sustained activation in right MFG. The interleaved context resulted in more antisaccade errors and slower prosaccade RTs which were restricted to switched trials within this context. Antisaccade switch trials showed the greatest BOLD signal change, notably within the ACC. These trials involved the most conflict between task sets for both stimulus-response mapping due to trial type instruction and task set reconfiguration due to trial history. The observed pattern of activation implies that the combination of these control processes created a unique demand for ACC involvement beyond what either process recruited independently. Cognitive control of saccade behavior, therefore, is sensitive to contextual contingencies surrounding task performance and can shape transient and sustained task activation to optimize behavior for both novel and habitual task sets.

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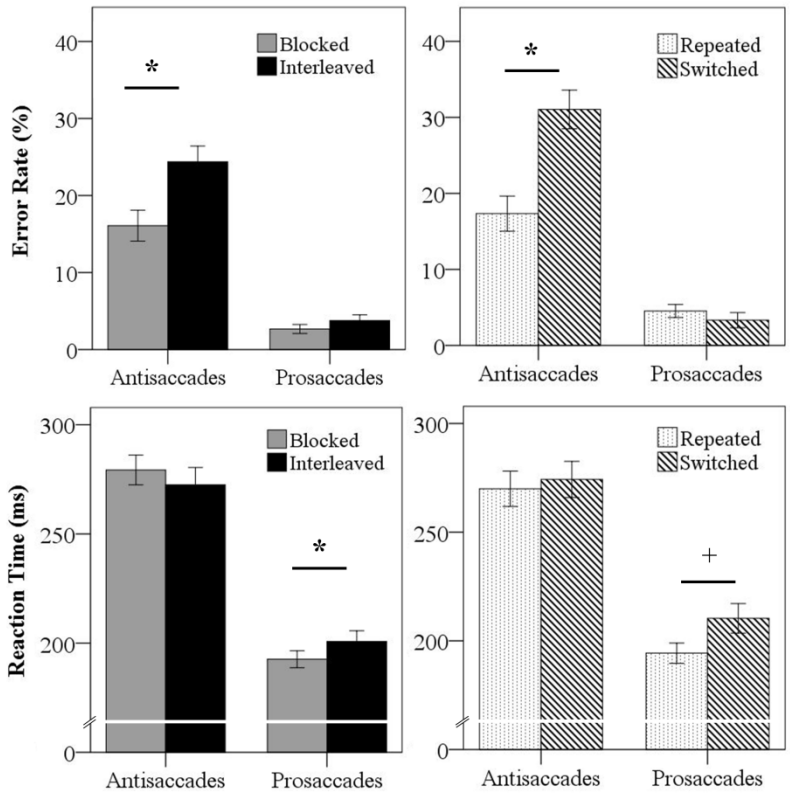


<u>Figure 2.1</u> Blocked versus interleaved behavior. Error rates and correct reaction times (mean/SE) for the blocked versus interleaved task context comparison (left) and the repeated versus switched trials comparison within the interleaved task (right). Antisaccade error rate in the interleaved task was higher than in the blocked task, and higher for switched antisaccade trials than repeated trials within the interleaved task. Prosaccade reaction time for correct trials exhibited a similar pattern with slower RT in the interleaved task than the blocked task, and slower RT for switched than repeated trials within the interleaved task. * denotes $p<.05$; + $p<.10$.

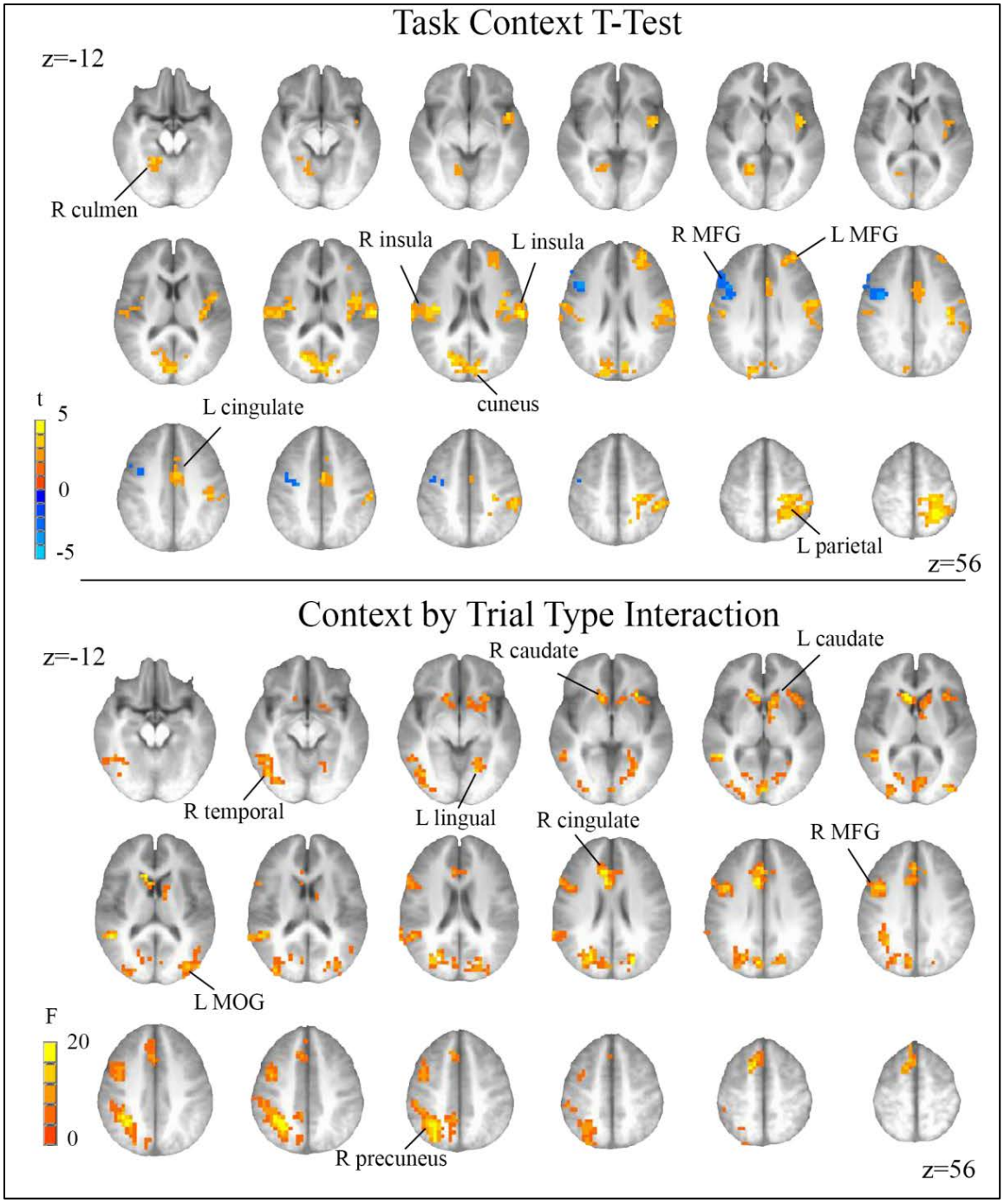
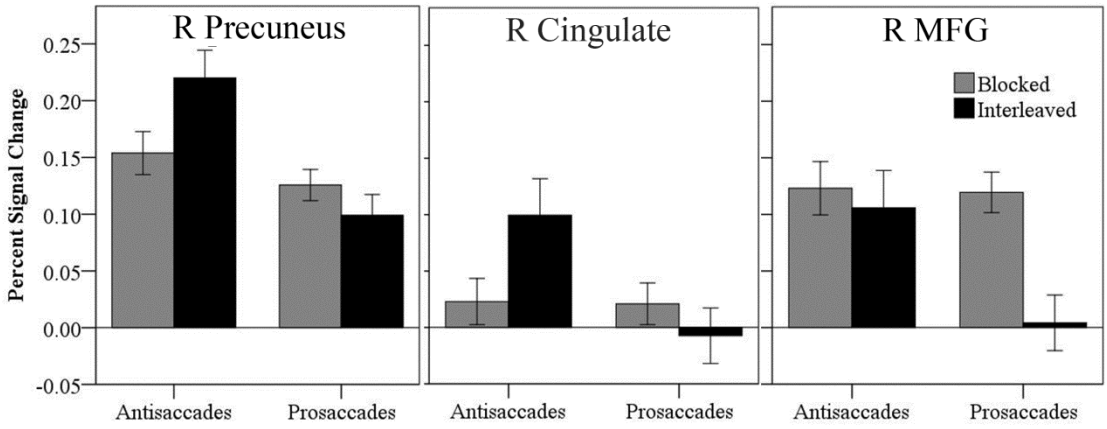


Figure 2.2 Statistical brain maps for the comparison of task context. Top: *t*-test between the blocked and interleaved tasks with warm colors representing greater BOLD signal in the interleaved task and cool colors representing greater BOLD signal in the blocked task. Bottom: interaction effect in the ANOVA on task context (blocked / interleaved) and saccade trial type

(antisaccade/ prosaccade) showing regions with significant difference between trial type activation in the two contexts; brighter colors represent higher *F*-values. Brain images are displayed in radiological convention with functional results (voxel-wise $p<.025$, family-wise $\alpha<.05$) overlaid on the average of the standardized anatomical images from all subjects. Details of the clusters are provided in Table 2.1.



<u>Figure 2.3</u> Average BOLD percent signal change from three representative clusters from the task context by trial type interaction. The right precuneus (as well as right temporal gyrus and left occipital cortex) had positive BOLD signal for all trial conditions, but with greater signal for antisaccade trials in the interleaved task; the right cingulate/SFG (and bilateral caudate) had positive BOLD signal for only the antisaccade trials in the interleaved task; the right MFG was the only region that showed positive BOLD signal for all conditions except the prosaccade trials in the interleaved task.

Anatomical Region	Peak Statistic Value	Peak Statistic Location (x, y, z)			Size (voxels)
Task context t-test	*t*-value				
Interleaved > blocked					
Left postcentral gyrus/ inferior parietal lobule	5.1	-26	-45	56	337
Left cingulate gyrus	3.3	-2	-1	36	54
Left superior/middle frontal gyrus	3.4	-26	39	24	47
Right postcentral gyrus/ insula	4.4	34	-13	20	85
Left insula	4.0	-38	-1	16	80
Bilateral cuneus	4.1	18	-69	20	125
Right culmen/ lingual gyrus	3.5	18	-53	4	61
Blocked > interleaved					
Right middle/inferior frontal gyrus	-3.6	42	11	24	64
Context by trial type interaction	F-value				
Right precuneus/ inferior parietal lobule	22.1	30	-49	40	337
Right inferior/middle frontal gyrus	15.6	42	7	28	108
Right cingulate/ superior frontal gyrus	31.0	6	11	24	141
Left middle occipital gyrus/ cuneus	18.2	-22	-73	24	73
Left caudate/ insula	19.9	-26	19	0	83
Right caudate	21.5	10	19	12	44
Left lingual gyrus	13.7	2	-81	4	60
Right superior/middle temporal gyrus	18.7	46	-45	12	129

Table 2.1 Description of the significant clusters for the task context *t*-test and context by trial type interaction. Coordinates refer to the Talairach-Tournoux atlas and voxel size is based on 4 mm^3 voxels.

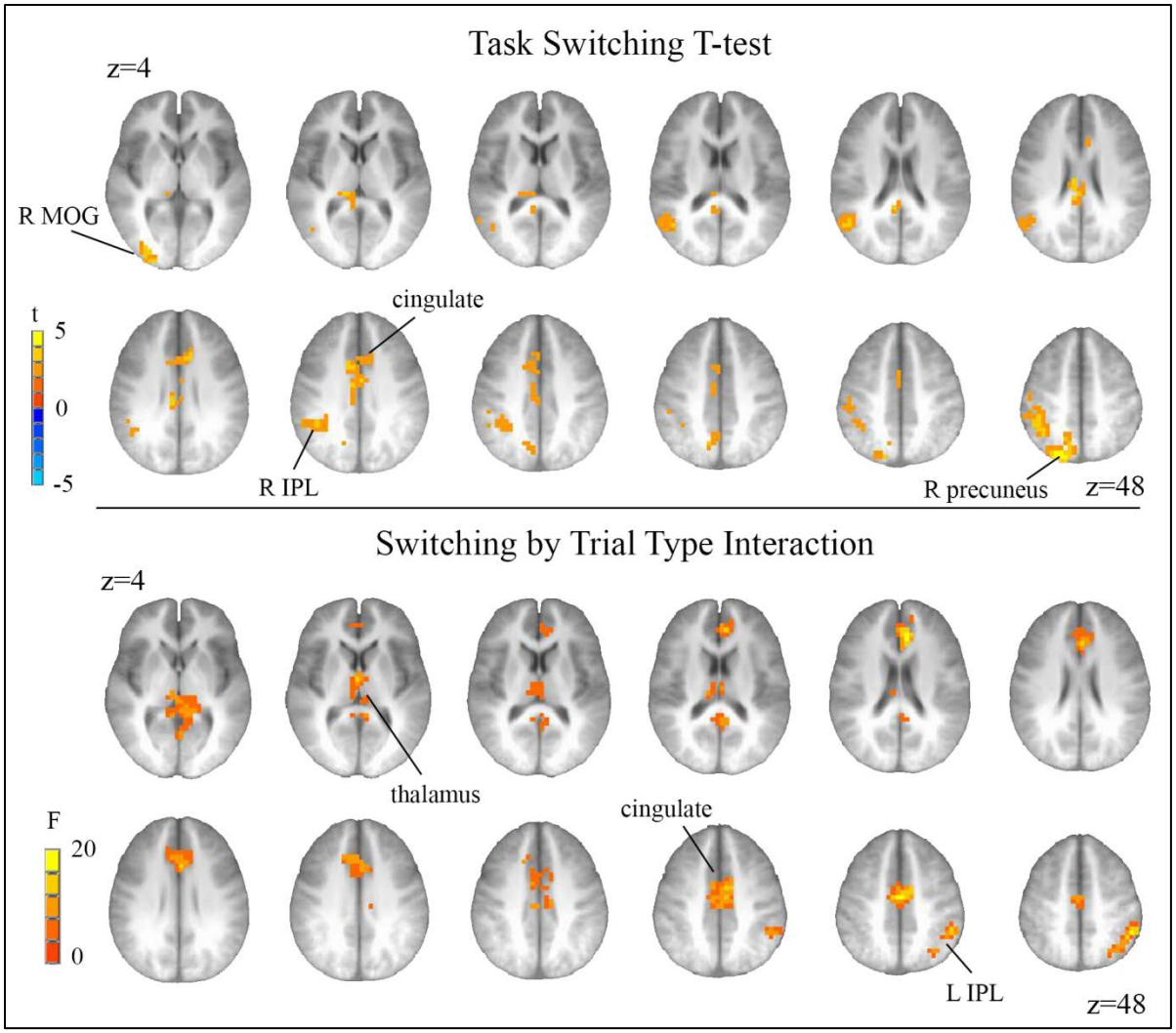
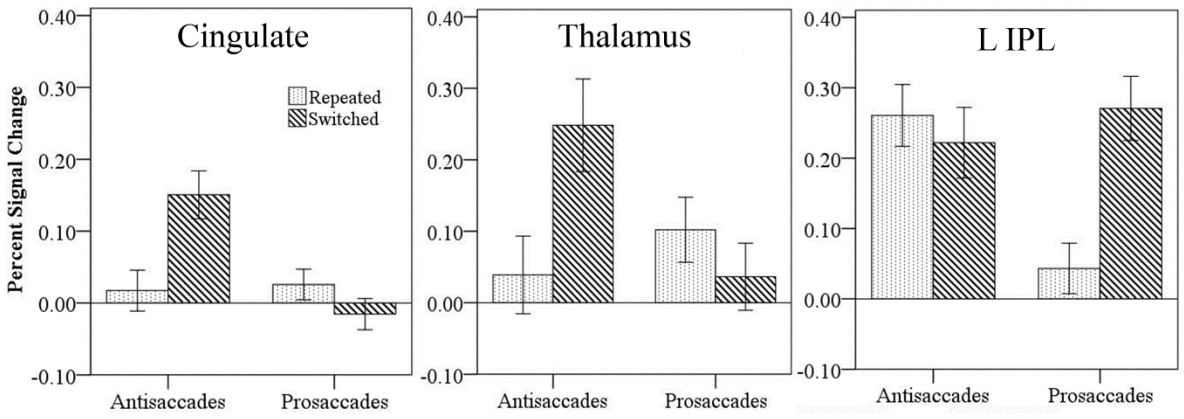


Figure 2.4 Statistical brain maps for the comparison of task switching in the interleaved task. Top: *t*-test between repeated and switched trials with warm colors representing greater BOLD signal on switched trials (no regions showed more signal for repeated trials). Bottom: interaction effect in the ANOVA on task switching (switched/repeated) and saccade trial type (antisaccade/ prosaccade) showing regions with significant difference between task switching conditions for the two trial types; brighter colors represent higher *F*-values. Brain images are displayed in radiological convention with functional results (voxel-wise $p<.025$, family-wise $\alpha<.05$) overlaid on the average of the standardized anatomical images from all subjects. Details of the clusters are provided in Table 2.2.



<u>Figure 2.5</u> Average BOLD percent signal change from clusters in the task switching by trial type interaction. The cingulate and thalamus showed the strongest BOLD signal for switched antisaccade trials, while the left IPL showed positive BOLD signal for all conditions except repeated prosaccades.

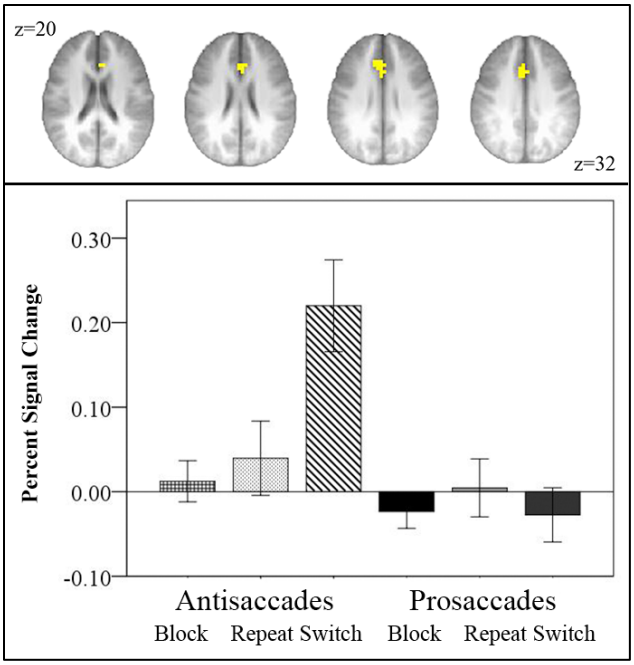


Figure 2.6 A conjunction map of the two interaction effects between task context or task switching and trial type. This analysis identified a cluster within the ACC for which the average BOLD signal change (mean/SE) for each trial condition is plotted. The ACC had positive BOLD signal for antisaccade switched trials in the interleaved task context, but no signal change during other trials.

Anatomical Region	Peak Statistic Value	Peak Statistic Location (x, y, z)			Size (voxels)
Task switching t-test	*t*-value				
Switched >repeated					
Right precuneus	4.5	22	-73	48	86
Right inferior parietal lobule/ superior temporal gyrus	4.7	38	-45	52	175
Bilateral cingulate	4.0	-10	19	28	112
Right middle/inferior occipital gyrus	4.2	26	-85	0	44
Switching by trial type interaction	*F*-value				
Left inferior/ superior parietal lobule	17.0	-46	-45	48	51
Bilateral cingulate	20.9	-6	31	20	194
Thalamus/ posterior cingulate	12.4	2	-9	8	116
Interaction conjunction					
Anterior cingulate	--	-2	23	20	28

Table 2.2 Description of the significant clusters for the task switching t-test, switching by trial type interaction, and the conjunction map. Coordinates refer to the Talairach-Tournoux atlas and voxel size is based on 4 mm^3 voxels.

CHAPTER 3

MODULATION OF COGNITIVE CONTROL LEVELS VIA MANIPULATION OF SACCADE TRIAL TYPE PROBABILITY ASSESSED WITH EVENT-RELATED BOLD FMRI[2]

[2] Pierce, J.E., & McDowell, J.E. (2016). *Journal of Neurophysiology, 115*(2), 763-772. Reprinted here with permission of publisher.

Abstract

Cognitive control supports flexible behavior adapted to meet current goals and can be modelled through investigation of saccade tasks with varying cognitive demands. Basic prosaccades (rapid glances towards a newly appearing stimulus) are supported by neural circuitry including occipital and posterior parietal cortex, frontal and supplementary eye fields, and basal ganglia. These trials can be contrasted with complex antisaccades (glances towards the mirror image location of a stimulus), which are characterized by greater functional MRI BOLD signal in the aforementioned regions and recruitment of additional regions such as dorsolateral prefrontal cortex. The current study manipulated the cognitive demands of these saccade tasks by presenting three rapid event-related runs of mixed saccades with a varying probability of antisaccade versus prosaccade trials (25, 50, or 75%). Behavioral results showed an effect of trial type probability on reaction time, with slower responses in runs with a high antisaccade probability. Imaging results exhibited an effect of probability in bilateral pre- and post-central gyrus, bilateral superior temporal gyrus, and medial frontal gyrus. Additionally, the interaction between saccade trial type and probability revealed a strong probability effect for prosaccade trials, showing a linear increase in activation parallel to antisaccade probability in bilateral temporal/occipital, posterior parietal, medial frontal, and lateral prefrontal cortex. In contrast, antisaccade trials showed elevated activation across all runs. Overall, this study demonstrated that improbable performance of a typically simple prosaccade task led to augmented BOLD signal to support changing cognitive control demands, resulting in activation levels similar to the more complex antisaccade task.

Introduction

Cognitive control allows for flexible adaptation of behavior to current goals. Optimal responding requires integration of external cues with internal action plans, as well as knowledge about previous occurrences of relevant stimuli. One means of investigating the complex interactions supporting cognitive control processes is via the ocular motor system underlying saccade generation. A saccade is a rapid eye movement made to foveate a location of interest in the visual field. Two commonly studied saccade types are basic prosaccades (glances towards a stimulus) and complex antisaccades (glances towards the mirror image location of a stimulus; Hallett, 1978), which represent lower and higher levels of cognitive control demands, respectively. This differentiation arises because antisaccade tasks require suppression of the natural tendency to look towards a newly appearing stimulus, transformation of the stimulus location into the opposite visual hemi-field, and volitional generation of a saccade to the appropriate location in the absence of a visual target (Hutton, 2008).

The cognitive demands of a saccade task including the context in which it is performed, affect individuals' behavioral responses. For example, generating antisaccades while completing a working memory task yields more failures of suppression (directional errors towards the stimulus) than performing the antisaccade task alone (Roberts et al., 1994), as these tasks putatively make demands upon similar neural resources. Cognitive demands also are altered by the trial composition within a task block: both prosaccade and antisaccade production are impacted by the relative proportion or probability of occurrence of each trial type (Chiau et al., 2011; Massen 2004; Pierce et al., 2015; Pierce and McDowell, 2016a). These studies demonstrated that when the probability of a given trial type was low, more errors were committed. Massen (2004) interpreted this result using a parallel programming/competition

model of saccade generation in which the appearance of a stimulus triggered the planning of both a prosaccade and an antisaccade (Cutsuridis et al., 2007; Massen, 2004; Noorani and Carpenter, 2013). During this competition, cognitive control processes acted to favor the appropriate response (and directly or indirectly suppressed the opposing task set; Everling and Johnston, 2013). When one trial type was more probable throughout a run its task set was strengthened by repeat performance and an expectation that it would occur again (Rogers and Monsell, 1995; Wylie et al., 2003). This task set bias may arise through an elevated level of baseline activity supporting the stimulus-response mapping, resulting in a reduction in the distance/time to reach motor threshold and thus fewer errors for that saccade type (Dorris and Munoz, 1998; Noorani and Carpenter, 2013). Conversely, the improbable occurrence of the other trial type led to a weakened task set representation such that when it did appear, its saccade program was poorly prepared and the opposing task set was prone to win the saccade competition, resulting in an erroneous response. Furthermore, reaction times (RTs) in such tasks were slowed when trial type probability was low (Chiau et al., 2011; Massen, 2004) or, alternately, when many antisaccade trials occurred (Pierce et al., 2015). In the latter case, it was hypothesized that repeated antisaccade performance generated residual motor suppression in the saccade system that led to slower subsequent responses, regardless of saccade type (Barton et al., 2006; Manoach et al., 2007; Pierce et al., 2015). The present study similarly varied the trial type probability of antisaccades and prosaccades in several mixed saccade runs to investigate the neural correlates of these behavioral differences in healthy young adults. When one saccade trial type occurred with low probability and its task set was engaged minimally prior to the trial, greater BOLD signal was expected as a reflection of the greater cognitive control required to select and execute the appropriate task set.

The neural circuitry underlying typical saccade production has been thoroughly described in humans using the blood oxygenation level dependent (BOLD) signal in functional magnetic resonance imaging (fMRI; e.g., Brown et al., 2006; Curtis and Connolly, 2008; Dyckman et al., 2007; Matsuda et al., 2004; Reuter et al., 2010). Fundamental regions of saccade circuitry include occipital cortex, posterior parietal cortex, frontal and supplementary eye fields, basal ganglia, thalamus, and superior colliculus. Greater strength or extent of activation in these regions and recruitment of additional regions including dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) occur when cognitive demands are high, such as in antisaccade tasks (Ettinger et al., 2008; Ford et al., 2005; Funahashi, 2014; McDowell et al., 2008; Munoz and Everling, 2004).

Multiple task requirements further modulate activation within saccade circuitry according to the specific cognitive demands of the paradigm. For example, posterior parietal regions are sensitive to sensorimotor calculations related to the peripheral stimulus location (Herweg et al., 2014); dlPFC is active when multiple task sets must be maintained and the correct stimulus-response mapping facilitated, notably in preparation for an antisaccade (Brown et al., 2007; DeSouza et al., 2003; Dyckman et al., 2007; Koval et al., 2014; Merriam et al., 2001). Additionally, parietal cortex and dlPFC respond to attentional demands (Corbetta and Shulman, 2002; Curtis et al., 2005; Petersen and Posner, 2012), spatial conflict (Cohen and Ridderinkhof, 2013), and working memory load (Braver et al., 1997). In Braver et al. (1997), fMRI BOLD signal increased linearly with working memory load, illustrating that cognitive control-related activation can mirror task demands and, thus, in the current study may respond in parallel to the increasing demand of highly probable antisaccade trials.

Models of cognitive control focus on the role of frontal regions, specifically emphasizing an interaction between dlPFC and ACC for supervising and executing task requirements (Ettinger et al., 2008; Ford et al., 2005; Johnston et al., 2007; MacDonald et al., 2000; Shenhav et al., 2013), although precise descriptions of each region's role differ across studies. Across various paradigms the ACC has been related to cognitive control processes including conflict monitoring (Botvinick et al., 2001), error processing (Polli et al., 2005), updating of an internal model (O'Reilly et al., 2013), task selectivity and difficulty (Johnston et al., 2007), and detection of low frequency events (Braver et al., 2001). This last feature is of particular relevance to the current manipulation because the ACC (along with dlPFC and parietal cortex) was shown to respond strongly when any of several cognitive tasks occurred with low frequency, but not when two trial types were equally probable (Braver et al., 2001). Top-down influences from these cognitive control regions may bias visual areas to exhibit greater activation when an unexpected stimulus appears (Kok et al., 2012; St John-Saaltink et al., 2015), potentially making such regions susceptible to contextual trial history and changes in trial type probability. Cognitive control and attentional regions may show activation to a greater extent in the current study either when one saccade trial type occurs with low probability or specifically when complex antisaccades occur with high probability, as both situations involve high cognitive demands. Greater BOLD signal in dlPFC, posterior parietal cortex, and ACC therefore can be conceptualized as indicative of greater cognitive control involvement in these saccade tasks to monitor and update internal task representations, attend to the appropriate stimulus location and select the correct task set.

In the current study, the trial type probability of antisaccades and prosaccades was varied across three runs with high, low, or equal probability of antisaccades to prosaccades.

Behaviorally, it was hypothesized that participants would make more antisaccade errors when antisaccade probability was low and that RTs for both antisaccades and prosaccades would be slower in runs with a higher probability of an antisaccade (Pierce et al., 2015). Neural responses, as indexed by the fMRI BOLD signal, were expected to reflect higher cognitive demands through increased activation in saccade circuitry. Specifically, when antisaccade trials were highly probable, increased demands for suppression and conflict monitoring were expected to increase activation in dlPFC and ACC for both saccade types in that run. When either trial type was improbable, posterior parietal regions were expected to increase activation to compensate for the higher attentional demands of the improbable trial type. Alternately, when both trial types were equally probable, participants might generate a stronger BOLD signal in these regions to respond under conditions of uncertainty. As such, the results will demonstrate which task conditions were most challenging as evidenced by poor behavioral performance and differential BOLD signal in saccade and cognitive control regions. Differing responses across levels of trial type probability imply that not only did the inherent demands of a cognitive task shape performance, but also the contextual conditions during which it was performed. A thorough understanding of how the brain responds to context changes for both simple (prosaccade) and more complex (antisaccade) tasks will illuminate how control mechanisms adaptively manage cognitive resources to optimize action in the varied conditions of daily life.

Methods

Participants

Sixty-five undergraduate students were recruited from the UGA Psychology Department online research pool and given course credit for their participation. Thirty individuals fulfilled

exclusion criteria or voluntarily opted out before completing the study. Thus data are reported from 35 right-handed, neurologically healthy participants (mean age = 19.5 years, SD = 3.5; 11 males), who experienced no current major psychiatric disorders or substance abuse, had no metal implants, and had normal or corrected-to-normal vision (via self-report). All participants provided written informed consent and activities were approved by the Institutional Review Board of the University of Georgia.

Task Design

The saccade task was composed of three runs with varying probability of occurrence of an antisaccade trial (relative to a prosaccade trial): 25%, 50%, or 75%. Each run consisted of 60 saccade trials presented according to the overall probability (e.g., 25% AS run had 15 antisaccade and 45 prosaccade trials), of which participants were not informed. All stimuli consisted of a 1° gray shape presented on a black background: during the fixations a cross appeared in the center of the screen for 2000 to 8000 ms (average 3500 ms). For saccade trials, the trial type cue was illuminated around the cross for 500 ms (for prosaccades, a square; for antisaccades, a diamond). This was followed by a blank screen for 200 ms ("gap" presentation) and finally the peripheral stimulus at +/- 5° or 10° from the center of the screen for 800 ms (Figure 3.1). Two peripheral stimulus eccentricities were included to reduce the likelihood of participants' anticipating the response location and preparing a motor response in advance (data collapsed across amplitude for analyses).

Procedure

Participants attended two separate sessions during the study: 1) a 30-minute screening session to determine if inclusion criteria were met, and 2) a one-hour MRI session. During the screening session, participants completed twenty practice trials (50% AS) of mixed prosaccades

("look as quickly and accurately as possible towards the peripheral stimulus") and antisaccades ("look to the mirror image location of the stimulus, opposite side, same distance from the center"). Those who satisfied inclusion criteria were scheduled for an MRI. During the MRI session, participants were positioned on the scanner table with the head secured. A high-resolution (T1-weighted) structural scan was obtained first for each participant, followed by the three functional runs (T2*-weighted). The functional saccade runs were counterbalanced and characterized by differing antisaccade probability (additional saccade runs were collected and not reported here). Stimuli were displayed using Presentation software (Neurobehavioral Systems, Albany, CA) and a dual mirror system attached to the head coil that allowed a participant to view a projection screen at his/her feet and researchers to monitor the participant's eye. The right eye position was captured by an infrared camera and transmitted to the researcher computer using the IView X MRI-LR system (SensoMotoric Instruments, Berlin, Germany). Pupil position was sampled at 60 Hz and recorded for off-line analysis. Before beginning the saccade tasks, eye position was calibrated using IView's 5-point calibration and an in-house horizontal calibration.

Imaging Parameters

MR images were collected on a 3T GE Signa Excite HDx system (General Electric Medical Systems, Milwaukee, WI) at the University of Georgia Bio-Imaging Research Center. A high-resolution anatomical image was collected using a T1-weighted 3D FSPGR sequence (inversion time (T1) = 450 ms, echo time (TE) = 3 ms, flip angle = 20°, field of view (FOV) = 240 mm x 240 mm, matrix size 256 x 256, 150 axial slices, in-slice resolution = 0.94 x 0.94 mm, slice thickness = 1.2 mm, slice gap = 0 mm, scan time=6:32). The three functional scans were collected using a T2*-weighted gradient echo EPI sequence (repetition time (TR) = 2000 ms, TE

= 30 ms, flip angle = 90°, FOV = 220 mm x 220 mm, matrix size = 64 x 64, 33 interleaved oblique slices, in-slice resolution = 3.4 x 3.4 mm, slice thickness = 4 mm, slice gap = 0 mm, scan time=5:24, 158 volumes plus 4 initial dummy scans to allow for magnet stabilization).

Analyses

Eye position data were scored using custom scripts written in MATLAB (MathWorks, Natick, MA). Trials were manually scored for initial direction of response (eye movements with velocities surpassing 20°/sec were classified as saccades) and reaction time (RT). Error rate was calculated as the number of trials with an initial saccade in the incorrect direction out of the total number of trials that met inclusion criteria; RT was defined as the time from the appearance of the peripheral circle to the initiation of the first saccade. Trials with no response, blinks at stimulus onset, anticipatory saccades (faster than 90 ms RT from peripheral stimulus onset or during the gap window), or with insufficient data quality due to loss of pupil tracking were excluded from further analyses. Based on these criteria, an average of 164 trials (SD=14) out of 180 per participant were included in the analysis. Statistical analyses on eye movement metrics were performed using SAS Version 5.1 (SAS Institute Inc., Cary, NC) and SPSS Version 21 (IBM Corp., Armonk, NY) software packages. A 2x3 (saccade trial type (anti/pro) by probability (25%, 50% or 75% AS)) repeated measures ANOVA was performed on error rate and RT for correct trials to quantify the effects of trial type probability on antisaccade and prosaccade behavior. Correlations were performed between error rate and RT for both trial types and between antisaccade error rate and prosaccade RT across all runs to assess the relationship between these behavioral indices with respect to trial type probability.

Functional MRI data were analyzed using the AFNI software package (Analysis of Functional NeuroImages; Cox, 1996; 2012) with initial processing steps including: slice-timing

correction, volume alignment to account for subject motion, resampling to 4 mm^3 voxel grid, spatial standardization to a Talairach template, spatial smoothing (4 mm full width-half maximum Gaussian kernel), and voxel-wise scaling to a mean of 100. Based on behavioral responses, individual subject data for each run were submitted to a general linear model with stimulus regressors for correct prosaccades, error prosaccades, correct antisaccades, and error antisaccades, as well as regressors of no interest to remove effects from baseline drift (linear, quadratic, cubic) and rotational movement in the x, y, and z planes. Stimulus regressors for each subject were generated by categorizing trials as correct or error based on the subject's responses and convolving the trial times (trial type cue presentation) in each correct/error category with a canonical gamma function representing the hemodynamic response (non-scored trials were not included in this categorization).

The group analysis was confined to regions within a custom brain mask created from the average gray matter segmentation from all subjects' anatomical images using FSL's FAST (FMRIB Software Libraries Automated Segmentation Tool; Zhang et al., 2001) in conjunction with putamen, caudate, and thalamus regions as defined by AFNI's Talairach-Tournoux atlas (Talairach and Tournoux, 1988). To protect against false positives resulting from multiple comparisons across voxels, a clustering method derived from Monte Carlo simulations was applied to the group maps. With a voxel-wise $p<.01$ (applied for main effects), a family-wise $\alpha<.05$ was preserved by clusters with a minimum of 24 voxels; with a voxel-wise $p<.025$ (interaction effect), a minimum of 47 voxels per cluster was required. Voxel-wise model coefficients for correct prosaccades and antisaccades were entered into a 2x3 (trial type (anti/pro) by probability (25%, 50%, or 75% AS)) repeated measures ANOVA. Post-hoc *t*-tests were performed on the cluster activations in each probability run to assess the nature of the overall

effects in greater detail. Correlations were performed between each subject's average beta coefficient (equivalent to percent signal change (afni.nimh.nih.gov)) from all voxels within each significant cluster identified in the interaction effect and the subject's error rate and RT. (One subject was removed from these correlations as a possible outlier inflating the magnitude of the correlations due to an antisaccade error rate more than 3 SDs above the mean in each of the three runs.)

Results

Behavioral Responses

The ANOVA results indicated that there were main effects of saccade trial type for both error rate ($F(1,34)=100.1$, $p<.01$, $\eta^2=.75$) and RT ($F(1,34)=196.2$, $p<.01$, $\eta^2=.85$), showing typical antisaccade costs of higher error rate and slower RT. There was no effect of probability on error rate ($F(2,68)=2.2$, $p=.11$), but there was a significant effect for correct trial RT ($F(2,68)=9.9$, $p<.01$, $\eta^2=.23$), where runs with a higher probability of antisaccades had slower RTs. The interaction between saccade trial type and probability was non-significant for error rate ($F(2,68)=1.1$, $p=.32$), but significant for RT ($F(2,68)=5.1$, $p<.01$, $\eta^2=.13$), with antisaccades showing a linear increase with probability. The average error rate and RT for prosaccade and antisaccade trials in each run are provided in Table 3.1. Across all three runs, individuals' antisaccade error rate moderately correlated with antisaccade RT ($r=-.22$, $p<.05$) and prosaccade RT ($r=-.36$, $p<.01$), such that higher error rates were associated with faster RTs.

Functional MRI Activation

Saccade Trial Type Main Effect

The main effect of trial type in the BOLD signal ANOVA indicated widespread differences in activation between prosaccades and antisaccades. A *t*-test on this trial type effect demonstrated the direction of the main effects (Figure 3.2 and Table 3.2). Canonical saccade regions showed greater activation for antisaccades including bilateral precentral gyrus (FEF), medial frontal gyrus (SEF/ACC), bilateral precuneus, bilateral middle frontal gyrus (dlPFC), and basal ganglia. Additional regions showed greater activation for prosaccades but that was largely driven by negative activation on antisaccade trials, including postcentral gyrus, posterior cingulate, bilateral superior temporal cortex, inferior medial frontal gyrus, and bilateral inferior occipital cortex.

Probability Main Effect

The ANOVA results yielded five regions of saccadic circuitry that significantly differentiated the three levels of trial type probability (25%, 50%, 75% AS). These clusters are displayed in Figure 3.3A and their characteristics listed in Table 3.2. They included bilateral pre- and post-central gyrus, bilateral superior temporal gyrus, and left medial frontal gyrus. These clusters encompassed regions of somatosensory and motor cortices, visual association processing regions in temporal cortex, and a portion of SEF extending into dorsal ACC. Post-hoc *t*-tests (Table 3.3) showed that BOLD signal in all clusters in the 75% AS run was significantly greater than the other two runs (25% and 50%), which did not differ from each other.

Trial Type by Probability Interaction

Finally, the interaction analysis between saccade trial type and probability identified four significant clusters including: precuneus extending into right middle occipital gyrus, a medial

frontal region consistent with SEF and extending into left superior frontal gyrus, left fusiform gyrus, and right inferior and middle frontal gyri (Figure 3.4A/Table 3.2). Post-hoc *t*-tests on the percent signal change from each of these clusters (Table 3.3) indicated that prosaccade activation in the 75% AS run was significantly higher than in the 25% run in all clusters, while antisaccade activation did not differ across runs (Figure 3.4B). Further, the prosaccade activation in three of the four clusters reached the level of antisaccade activation in the 75% AS run. These differential prosaccade activation patterns did not correlate with behavioral measures, perhaps due to a limited range of behavioral performance on prosaccade trials. Activation associated with antisaccade trials in the 50% AS run from the precuneus (r=-.41, p<.05) and SEF (r=-.41, p<.05) clusters was negatively correlated with error rate (Figure 3.5) – greater BOLD signal was associated with lower error rates. No effects were observed in relation to RT for prosaccades or antisaccades.

Discussion

This study investigated the effects of changing implicit saccade trial type probability on behavioral responses and fMRI BOLD signal in three rapid event-related runs of mixed antisaccades and prosaccades that draw upon cognitive control processes. Overall, the results demonstrated that when antisaccade trials occurred with high probability, antisaccade RTs were slower and BOLD signal was greater in regions of temporal, posterior parietal, medial frontal, and lateral prefrontal cortices. Furthermore, this probability-modulated BOLD signal originated primarily from prosaccade trials, for which activation in the high antisaccade probability run (75% AS) approached antisaccade activation levels (which did not differ with probability). This pattern suggests that when difficult antisaccade trials were probable, cognitive control demands

were high during all trials in that run, whereas when antisaccades were improbable, cognitive control was allocated more specifically to the demanding antisaccade trials themselves.

Behavioral Characteristics

Behavioral results indicated an overall effect of saccade trial type probability on RT with slower responses on all saccades in runs with a higher probability of antisaccades. This result is broadly consistent with the findings of Pierce et al. (2015), where runs with high antisaccade probability had slower RTs, especially following a previous antisaccade trial. Both studies support the conclusions of Barton and colleagues (2006) that motor suppression from antisaccade trials shapes the response profile of subsequent trials towards slower, more volitionally controlled saccades. Error rate, in contrast, did not differ significantly according to trial type probability. The negative correlation between antisaccade error rate and pro-and anti-saccade RT over the three runs combined, however, suggests that individuals who were faster to respond to the visual stimuli were prone to making more directional errors, whereas slower responders were able to successfully suppress the unwanted stimulus-directed saccade more often. The negative relationship between antisaccade error rate and prosaccade RT supports competition models of saccade generation (Cutsuridis et al., 2007; Massen, 2004; Noorani and Carpenter, 2013) by indicating that when a prosaccade can be programmed more quickly it is more likely to be performed as an antisaccade error, in agreement with previous reports (Reilly et al., 2008; Schaeffer et al., 2015). Thus, in runs with more probable antisaccade trials, participants were more likely to perform correctly if they responded slowly to the peripheral stimuli.

Antisaccade versus Prosaccade BOLD Signal

Results from the overall trial type comparison revealed numerous regions with stronger BOLD signal for antisaccade than prosaccade trials across runs including frontal and

supplementary eye fields, posterior parietal cortex, ACC, dlPFC, basal ganglia, thalamus, and anterior insula, as reported in previous studies (e.g., Brown et al., 2007; Curtis and D'Esposito, 2003; Ford et al., 2005; McDowell et al., 2008). This activation has been found consistently to support the preparation for and execution of a cognitively complex antisaccade task. There were several regions that exhibited greater BOLD signal for prosaccade trials including posterior cingulate, superior temporal gyrus, medial frontal gyrus, and inferior occipital gyrus, some of which are similar to previously reported regions (Ford et al., 2005; Krafft et al., 2012). Most of these regions revealed a pattern of positive activation during prosaccade trials combined with negative activation during antisaccade trials, perhaps suggesting top-down suppression of visual processing.

Neural Correlates of Trial Type Probability

Comparisons of activation between the three runs with varying probability of an antisaccade trial revealed several clusters in superior temporal, anterior parietal, and posterior frontal cortices that yielded greater BOLD signal when antisaccade trials were highly probable (i.e., 75% AS run). Inspection of the interaction between saccade trial type and probability further showed differences in bilateral temporal/occipital, posterior parietal, medial frontal, and lateral prefrontal cortices that showed a marked effect of trial type probability only for prosaccades. For antisaccades, activation in these regions showed no distinct pattern relative to probability. Indeed, prosaccade activation in the 75% AS run in the identified clusters approached the levels observed during antisaccade trials in these regions.

Differences in temporal/occipital clusters as well as posterior parietal cortex may have been caused by increased visual attention processing of the cue/stimulus - an orienting response (Braver et al., 2001; Corbetta and Shulman, 2002; Petersen and Posner, 2012) - when a trial type

was improbable. Posterior parietal regions have been associated previously with effects of "surprise" from a change in peripheral stimulus location (O'Reilly et al., 2013) and increased attentional demands in tasks that required reprogramming of saccades (Curtis et al., 2005). These deviations from predictable events cause re-orienting of attention to monitor more closely the subsequent visual stimuli (Petersen and Posner, 2012). Unexpected prosaccades trials in the 75% AS run likely elicited an attentional response in the midst of many antisaccade trials that could have modulated the responsiveness of visual cortices for the trial type cue and upcoming peripheral stimulus (Summerfield and Egner, 2009). Cues have been shown to enhance visual activity for an anticipated stimulus location (Kastner et al., 1999; Liu et al., 2005) or task set modality (Elkhetali et al., 2015), possibly as a result of top-down frontal-parietal signals influencing neural sensitivity or tuning (Carrasco, 2011; Summerfield and Egner, 2009). In the current results, an improbable prosaccade trial type cue would not match contextual expectations in the 75% AS run, would require greater processing of the cue to engage the appropriate task set and could result in increased sensitivity to the peripheral stimulus to aid a visually-driven motor response. Activation differences in somatosensory and motor cortices that are not part of typical saccade circuitry may have resulted from an attention-related increase in the extent of saccade circuitry that spread to adjacent regions (Luna et al., 1998).

Prosaccade trials in the 75% AS run resulted in activation in SEF and lateral PFC, possibly reflecting a greater need for cognitive control on these improbable trials. These cortical areas typically show a greater BOLD signal for antisaccade trials than prosaccade trials (as was the case for the 25% AS run; Brown et al., 2007; Curtis and D'Esposito, 2003; Ford et al., 2005; McDowell et al., 2008), but improbable prosaccade trials showed strong activation as well. Greater PFC activation for improbable prosaccade trials might facilitate the prosaccade task set

(Everling and Johnston, 2013) that was suppressed by repeated antisaccade performance. Another possibility is that the 75% AS run required higher levels of cognitive control throughout the run (Dyckman et al., 2007) because of the high probability of performing complex antisaccades. Greater BOLD signal in SEF and PFC then resulted from a need for stronger top-down biases on visual processing or from latent suppression of saccade motor regions (Brown et al., 2007; Ford et al., 2005; Miller and Cohen, 2001; Munoz and Everling, 2004). In this interpretation, top-down influences from highly probable antisaccade trials produced an elevated BOLD signal throughout the run as individuals modulated their expectations for high cognitive demands (cf. Klein et al., 2014).

The increased activation for prosaccade trials in the 75% AS run raises the question: why do antisaccades in the 25% AS run not exhibit a similar increase in activation when they are improbable? The answer may lie in the inherent asymmetry (Barton et al., 2006; Monsell et al., 2000) between the two tasks: a prosaccade is a naturally frequent action, corresponds to a direct stimulus-response mapping and typically has minimal cognitive demands. An antisaccade is a complex action, corresponds to an arbitrary stimulus-response mapping and requires cognitive control regardless of context. Thus, when the antisaccade task is improbable participants may not need or be able to augment cognitive control and spatial attention processes (and their associated neural substrates) beyond normal task levels. The challenging antisaccade task, therefore, appears to be less sensitive to context than the simple prosaccade task.

The asymmetric cognitive control demands for antisaccade trials also resulted in greater activation across all runs compared to prosaccade trials in the ACC, consistent with the greater inherent conflict or need for performance evaluation in this task (Ford et al., 2005; MacDonald et al., 2000; Matsuda et al., 2004; McDowell et al., 2008; Miller and Cohen, 2001). (As error trials

were excluded from these analyses, it is unlikely that this signal originated directly from processing of antisaccade error commissions.) Additionally, the trial type probability manipulation modulated a portion of the dorsal ACC and supplementary motor area, increasing BOLD signal when antisaccades were more probable. The observed pattern supports the interpretation that the ACC responds to increased cognitive demands (Johnston et al., 2007) and response selection (Cohen and Ridderinkhof, 2013), implying that the 75% AS run required the greatest cognitive control for the challenging combination of probable antisaccade trials and improbable prosaccade trials.

As the trial type probability effect was most evident for prosaccade trials, this activation could reflect greater competition between a visual grasp reflex (Hess et al., 1946; Theeuwes et al., 1998) and the need to apply specific task set rules based on the context (Dyckman et al., 2007; Everling et al., 1998). On antisaccade trials, this conflict was high in all conditions, but for prosaccades the competition was especially salient when prosaccades were improbable (Braver et al., 2001). Thus when an improbable prosaccade cue did appear, participants had to attend to this cue and retrieve its stimulus-response mapping in a more effortful, controlled manner (Hutton, 2008; Stuyven et al., 2000) than when prosaccades were highly probable. The greater BOLD signal measured in frontal-parietal attention regions, saccade eye fields, and secondary visual processing regions, therefore, could be a result of instantiating greater control of prosaccade generation on improbable trials.

Brain-Behavior Correlations

When comparing the changes in BOLD signal with behavioral performance, antisaccade error rate showed a negative relationship with percent signal change in the SEF and precuneus clusters from the ANOVA interaction: more signal on antisaccade trials in the 50% AS run

corresponded with fewer errors. Although antisaccade error rate and BOLD signal did not differ with trial type probability, these correlations imply that individuals who engaged more neural resources according to the cognitive control demands of the task had fewer failures of suppression. Prosaccade behavior did not exhibit any relationship with activation in these regions of trial type probability effects. This could be due to the fact that prosaccade behavioral performance is less variable overall and most individuals are able to perform near ceiling in all conditions. Yet this makes the differences in prosaccade BOLD signal relative to probability all the more interesting: even though individuals are able to generate the same fast, correct responses, the brain must work harder (perhaps especially during saccade preparation after seeing the trial type cue) to produce this response, thus generating a stronger BOLD signal. This highlights an advantage of using neuroimaging to investigate saccades and cognitive control – paradigm manipulations that yield small or negligible behavioral effects may yet entail a neural cost. Similar behavioral outcomes can mask significant differences in how the brain responds to a cognitive task.

One limitation of this study stems from the fact that varying the probability of each trial type resulted in an uneven number of trials across conditions. This could reduce the reliability or strength of parameter estimates for improbable trials. An inspection of the data, however, suggests that the impact of this difference was minimal as the variability of the BOLD signal was comparable across conditions and improbable trials did not contribute a weak, unstable signal.

Conclusions

The current study investigated behavioral responses and BOLD signal changes with manipulation of cognitive control via saccade trial type probability in three rapid event-related fMRI runs of mixed antisaccades and prosaccades. Task demands from antisaccade trials activate

saccadic circuitry to a greater extent than prosaccade trials under most task conditions. In the current study, however, improbable prosaccade trials required increased BOLD signal in visual attention and saccade control regions. Prosaccade BOLD signal for those improbable trials was comparable to antisaccade levels and potentially related to effortful selection of the appropriate task set for this usually stimulus-driven behavior. Antisaccade activation itself did not exhibit a clear relationship with trial type probability, perhaps because the complex antisaccade task set always strongly conflicts with the natural prosaccade tendency. Overall, the conditions in which saccades were performed influenced the BOLD signal of a simple task more extensively than a complex task as participants responded to changing cognitive demands and altered the degree of cognitive control applied to achieve successful task performance. Clarifying how saccadic circuitry responds to implicit variations in saccade task conditions can illuminate how cognitive control mechanisms are functionally implemented and, thus, how individuals are able to adapt to changing environmental demands in everyday activities.

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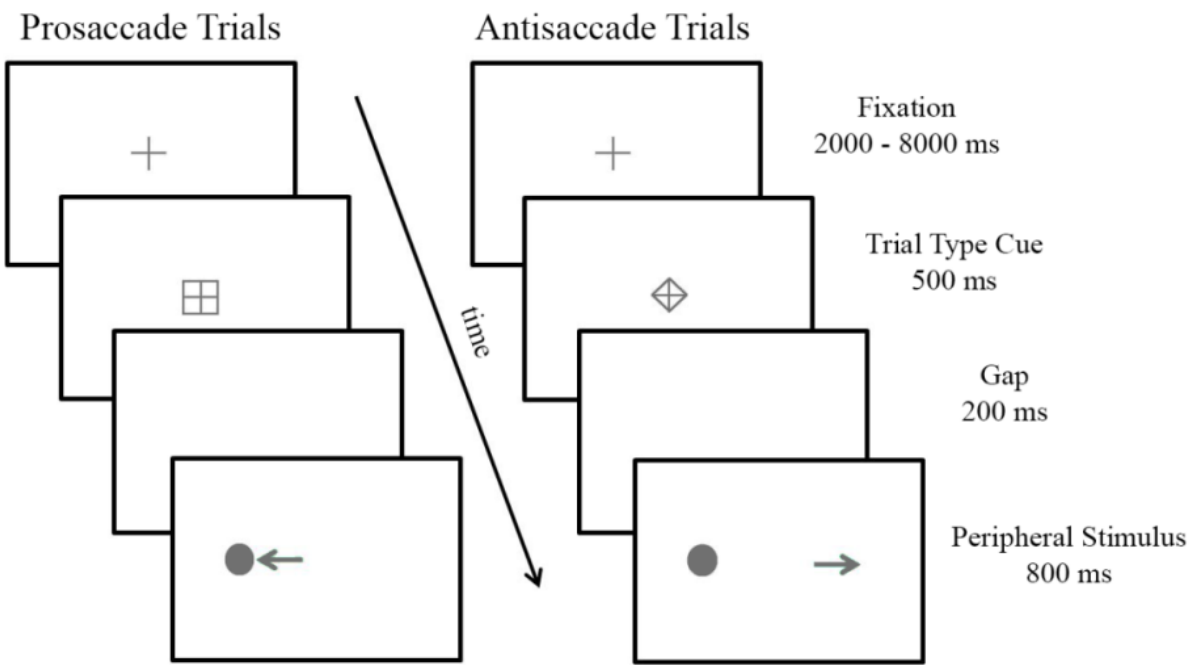


Figure 3.1 Stimulus design and timing. Between each trial participants viewed a central fixation cross for a variable period to allow for deconvolution of the stimulus-related hemodynamic response in the rapid event-related design. The trial proper began with the trial type cue (square or diamond), followed by a gap screen and finally the peripheral circle, with presentation times as shown. The arrow indicates the direction of correct responses and did not appear during the trials.

	Error Rate (%)	Reaction Time (ms)
Prosaccades		
25% AS	3.0 (4.2)	190 (23)
50% AS	3.4 (3.8)	200 (26)
75% AS	2.3 (5.0)	197 (29)
Antisaccades		
25% AS	26.9 (18.1)	266 (41)
50% AS	27.5 (14.5)	273 (41)
75% AS	23.5 (13.4)	285 (40)

Table 3.1 Average error rate and correct reaction time for prosaccade and antisaccade trials. Values are given as mean (SD).

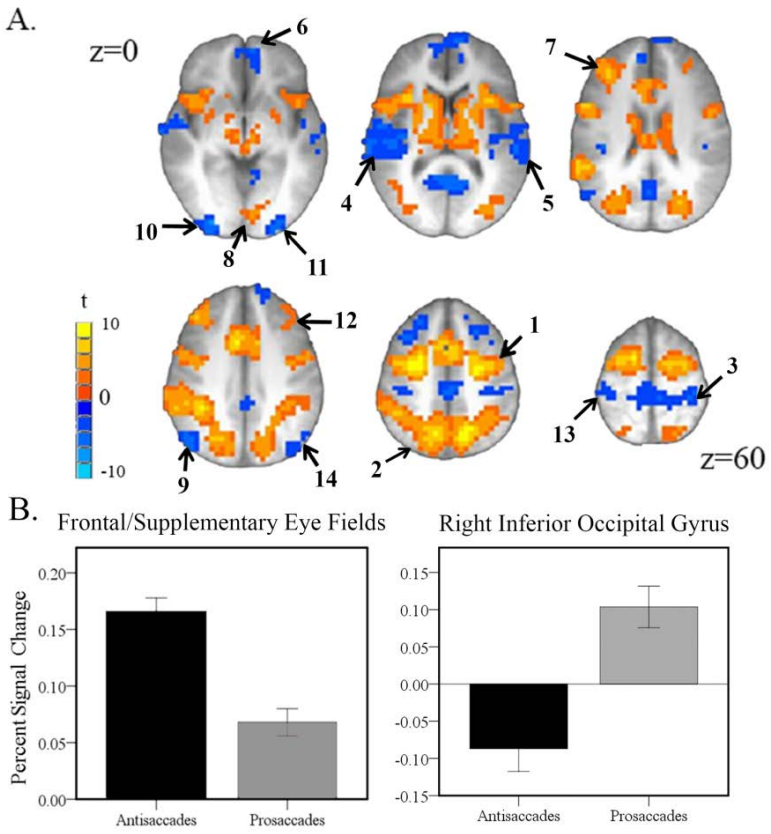


Figure 3.2 Main effect of saccade trial type. *(A)* T-test for trial type effects revealed multiple clusters differentiating the prosaccade and antisaccade trials (voxel-wise $p<.01$, family-wise $\alpha<.05$). As consistent with previous literature, warm colors indicate greater activation for antisaccades. Cool colors, here, indicate greater activation for prosaccades. Brain images are displayed in radiological convention with functional results overlaid on the average of the standardized anatomical images from all subjects. *(B)* Average BOLD percent signal change (mean/SE) from a cluster incorporating the frontal and supplementary eye fields (cluster 1), representative of areas showing stronger activation for antisaccade than prosaccade trials, and a cluster in right inferior occipital gyrus (cluster 10) representative of stronger/positive activation for prosaccade trials and weaker/negative activation for antisaccade trials. The number labels in 3.2*A* correspond to the numbers in Table 3.2 and identify clusters plotted in 3.2*B*.

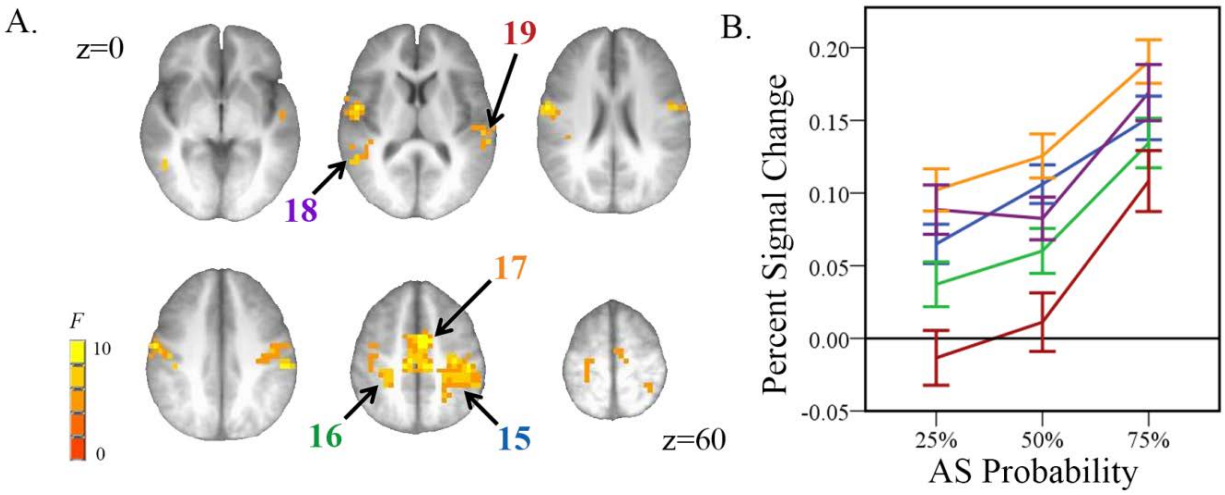
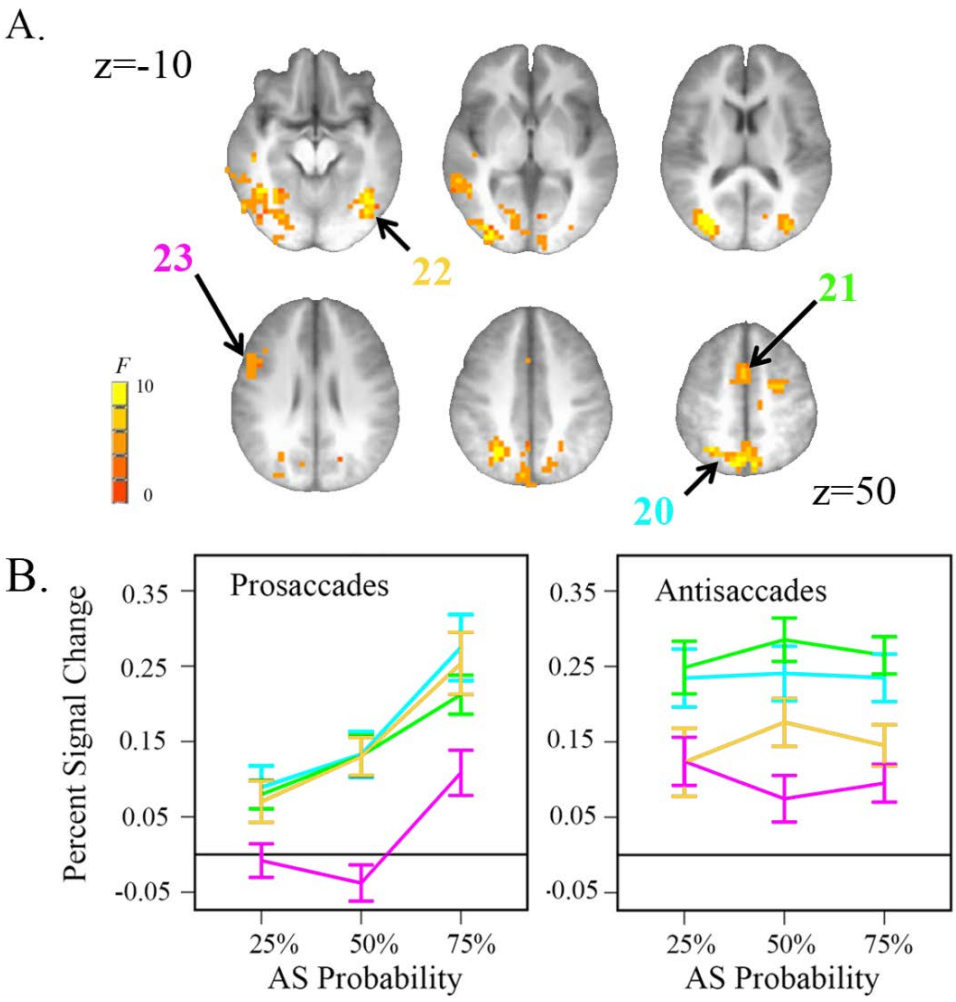


Figure 3.3 Main effect of probability for correct prosaccade and antisaccade trials. *(A)* Five significant clusters differentiated between the probability conditions (voxel-wise $p<.01$, family-wise $\alpha<.05$): 15) left pre/postcentral gyrus, 16) right pre/postcentral gyrus, 17) left medial frontal gyrus/cingulate, 18) right superior temporal gyrus, and 19) left superior temporal gyrus. Brain images are displayed in radiological convention with functional results overlaid on the average of the standardized anatomical images from all subjects. *(B)* Average BOLD percent signal change (mean/SE) for each of the clusters in the three runs. The colors of the number labels in 3.3*A* correspond to the lines plotted in 3*B* and the details of each cluster that are provided in Table 3.2.



<u>Figure 3.4</u> Trial type by probability interaction for correct prosaccade and antisaccade trials. *(A)* Four clusters demonstrated a probability effect for prosaccade trials, with minimal differences between runs for antisaccade trials (voxel-wise $p<.025$, family-wise $\alpha<.05$): 20) precuneus/ right middle occipital gyrus, 21) medial/superior frontal gyrus, 22) left fusiform gyrus, and 23) right inferior/middle frontal gyrus. Brain images are displayed in radiological convention with functional results overlaid on the average of the standardized anatomical images from all subjects. *(B)* Average BOLD percent signal change (mean/SE) for each of the interaction clusters. The colors of the number labels in 3.4*A* correspond to the lines plotted in 3.4*B* and the details of each cluster that are provided in Table 3.2.

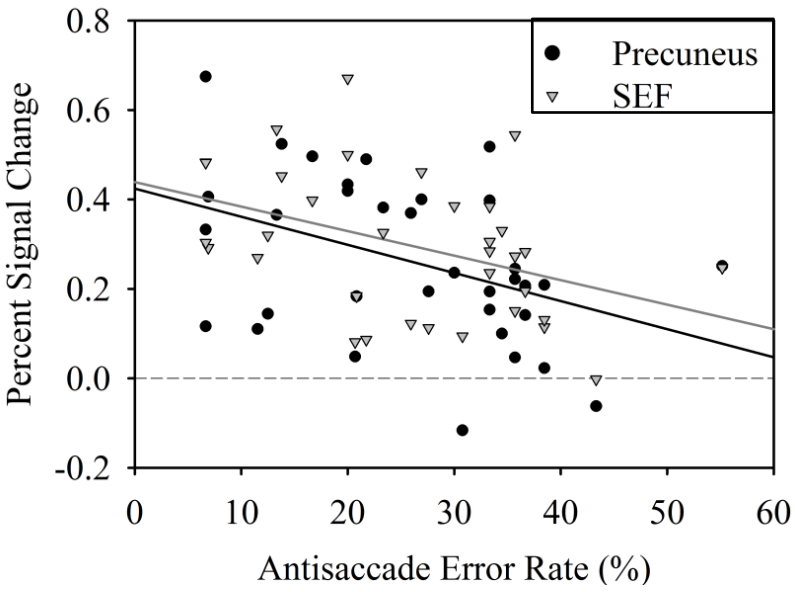


Figure 3.5 Correlation between antisaccade error rate and BOLD signal in the 50% AS run. Two clusters (precuneus and SEF) in the saccade trial type by probability interaction showed significant negative correlations such that participants who committed fewer antisaccade errors had higher activation in these regions.

Anatomical Region	Peak Statistic	Peak Statistic Location (x, y, z)			Size (voxels)
Trial Type Main Effect (T-test)	*t*-value				
1) Bilateral Precentral Gyrus/Cingulate/ Basal Ganglia	9.92	22	-5	48	1705
2) Bilateral Precuneus/Inferior Parietal Lobule	9.37	-14	-65	48	1131
3) Postcentral Gyrus/Posterior Cingulate/ Paracentral Lobule	-5.76	-6	-53	12	329
4) Right Superior Temporal Gyrus/Insula	-6.31	38	-17	16	216
5) Left Superior Temporal Gyrus/Insula	-4.86	-58	-9	-8	158
6) Medial Frontal Gyrus	-4.35	6	55	16	133
7) Right Middle Frontal Gyrus	6.55	34	31	32	102
8) Left Lingual Gyrus/ Cerebellum	4.52	-30	-57	-20	92
9) Right Angular Gyrus	-5.34	46	-61	28	52
10) Right Inferior Occipital Gyrus/ Lingual Gyrus	-6.97	22	-89	-4	49
11) Left Inferior Occipital Gyrus/ Lingual Gyrus	-6.26	-22	-89	-4	42
12) Left Middle Frontal Gyrus	4.01	-30	39	32	41
13) Right Postcentral Gyrus	-3.99	38	-21	60	41
14) Left Precuneus/Angular Gyrus	-3.92	-38	-73	36	24
Probability Main Effect	*F*-value				
15) Left Pre/Postcentral Gyrus	10.38	-54	-25	36	183
16) Right Pre/Postcentral Gyrus	11.02	54	-5	16	142
17) Left Medial Frontal Gyrus/Cingulate	11.22	-6	-5	48	87
18) Right Superior Temporal Gyrus	9.40	50	-45	16	47
19) Left Superior Temporal Gyrus	7.97	-54	-25	8	34
Trial Type by Probability Interaction					
20) Precuneus/ Right Middle Occipital Gyrus	12.83	30	-73	16	677
21) Medial/Superior Frontal Gyrus	7.62	-18	-9	52	58
22) Left Fusiform Gyrus	11.17	-38	-57	-8	52
23) Right Inferior/Middle Frontal Gyrus	9.3	46	11	32	48

Table 3.2 Description of the significant clusters for the trial type by probability ANOVA.

Coordinates refer to the Talairach-Tournoux atlas and voxel size is based on 4 mm^3 voxels.

Probability Main Effect			
	25% AS vs. 50% AS	25% AS vs. 75% AS	50% AS vs. 75% AS
15) L Pre/Postcentral	t(69) = -2.3, p=.02	**t(69) = -4.3, p<.001**	**t(69) = -2.7, p=.008**
16) R Pre/Postcentral	t(69) = -1.2, p=.24	**t(69) = -4.8, p<.001**	**t(69) = -4.1, p<.001**
17) L MFG/Cingulate	t(69) = -1.2, p=.25	**t(69) = -4.1, p<.001**	**t(69) = 3.7, p<.001**
18) R Superior Temporal	t(69) = 0.3, p=.75	**t(69) = -3.5, p=.001**	**t(69) = -4.7, p<.001**
19) L Superior Temporal	t(69) = -0.9, p=.37	**t(69) = -4.0, p<.001**	**t(69) = -3.4, p=.001**
Trial Type by Probability Interaction			
Prosaccades	25% AS vs. 50% AS	25% AS vs. 75% AS	50% AS vs. 75% AS
20) Precuneus/ R MOG	t(34) = -1.1, p=.30	**t(34) = -3.6, p=.001**	t(34) = -2.8, p=.01
21) Med/Sup Frontal	t(34) = -1.6, p=.11	**t(34) = -4.1, p<.001**	t(34) = -2.6, p=.01
22) L Fusiform	t(34) = -1.7, p=.11	**t(34) = -4.2, p<.001**	t(34) = -2.6, p=.01
23) R Inf/Mid Frontal	t(34) = 0.9, p=.39	**t(34) = -3.4, p=.002**	**t(34) = -4.6, p<.001**
Antisaccades	25% AS vs. 50% AS	25% AS vs. 75% AS	50% AS vs. 75% AS
20) Precuneus/ R MOG	t(34) = -0.1, p=.90	t(34) = -0.1, p=.99	t(34) = 0.1, p=.90
21) Med/Sup Frontal	t(34) = -1.1, p=.29	t(34) = -0.4, p=.70	t(34) = 0.7, p=.51
22) L Fusiform	t(34) = -1.1, p=.27	t(34) = -0.4, p=.68	t(34) = 0.7, p=.51
23) R Inf/Mid Frontal	t(34) = 1.2, p=.25	t(34) = 0.7, p=.48	t(34) = -0.7, p=.49
Pro vs. Anti	25% AS	50% AS	75% AS
20) Precuneus/ R MOG	**t(34) = -4.7, p<.001**	**t(34) = -3.2, p=.003**	t(34) = 1.3, p=.19
21) Med/Sup Frontal	**t(34) = -5.6, p<.001**	**t(34) = -6.7, p<.001**	t(34) = -2.3, p=.03
22) L Fusiform	t(34) = -1.4, p=.17	t(34) = -1.7, p=.10	**t(34) = 3.9, p<.001**
23) R Inf/Mid Frontal	**t(34) = -4.2, p<.001**	**t(34) = -4.1, p<.001**	t(34) = 0.5, p=.64

Table 3.3 Post hoc *t*-tests on BOLD activation in significant clusters for probability main effect and trial type by probability interaction. Significant differences ($p<.01$) are shown in bold.

CHAPTER 4

REDUCED COGNITIVE CONTROL DEMANDS FOLLOWING PRACTICE OF SACCADE TASKS IN A TRIAL TYPE PROBABILITY MANIPULATION[3]

[3] Pierce, J.E., & McDowell, J.E. submitted to *Journal of Cognitive Neuroscience,* 7 Apr 2016.

Abstract

Cognitive control is engaged to facilitate stimulus-response mappings for novel, complex tasks and supervise performance in unfamiliar, challenging contexts – processes supported by prefrontal cortex (PFC), anterior cingulate cortex (ACC), and posterior parietal cortex (PPC). With repeated task practice, however, the appropriate task set can be selected in a more automatic fashion with less need for top-down cognitive control and weaker activation in these brain regions. One model system for investigating cognitive control is the ocular motor circuitry underlying saccade production, where basic prosaccade trials (look towards a stimulus) can be contrasted with complex antisaccade trials (look to mirror image location). Previous studies have shown behavioral improvements on saccade tasks following practice with contradictory results regarding the direction of functional MRI BOLD signal change. The current study presented healthy young adults with prosaccade and antisaccade trials in five mixed blocks with varying probability of each trial type (0, 25, 50, 75, or 100% anti vs. pro) at baseline and post-test MRI sessions. Between the scans, participants practiced either the specific probability blocks used during testing or only a general 100% antisaccade block. Results indicated an overall reduction in BOLD signal within PFC, ACC, and PPC and across saccade circuitry for antisaccade trials. The specific practice group showed additional regions including ACC, insula, and thalamus with a BOLD decrease following practice, while the general practice group showed little change in those regions. These findings demonstrate that cognitive control regions recruited to support novel task behavior were engaged less following practice, especially with exposure to mixed task contexts rather than a novel task in isolation.

Introduction

Cognitive control is a term encompassing multiple supervisory processes that coordinate sensory and motor functions to flexibly adapt behavior to current goals (Braver, Paxton, Locke, & Barch, 2009; Cole & Schneider, 2007; Diamond, 2013; Fernandez-Duque & Knight, 2008; Miller & Cohen, 2001). This often requires facilitation of new, unfamiliar task rules over habitual, familiar responses. In order to learn the appropriate stimulus-response associations for a new task or context, a cognitive control "scaffolding" system involving prefrontal cortex (PFC), anterior cingulate cortex (ACC), and posterior parietal cortex (PPC) is recruited across cognitive paradigms (Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005; Chein & Schneider, 2005; Kelly & Garavan, 2005). With repeated exposure to or practice of a task, however, activation measured with the blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) signal typically is reduced in cognitive control and attentional networks over time (Chein & Schneider, 2005). Presumably, novel tasks recruit large neural populations to establish an unfamiliar task set, while over time a more focal set of neurons are sufficient to produce the correct response (Kelly & Garavan, 2005; Poldrack, 2000). This occurs once task rules are learned and relevant connections strengthened, so that neural networks can perform the requisite processing more efficiently (Bassett, Yang, Wymbs, & Grafton, 2015).

One model system for studying cognitive control and changes following task practice is the ocular motor circuitry associated with saccade production. Saccades are rapid eye movements made to foveate a location of interest in the visual field. Visually-guided prosaccades (look towards a newly appearing stimulus) can be contrasted with volitionally-driven antisaccades (look to the mirror image location of a stimulus). The need to suppress a saccade towards the stimulus, to transform the spatial location of the stimulus into the opposite visual

field, and to facilitate an endogenous saccade to a blank location during an antisaccade trial require higher levels of cognitive control than a prosaccade trial (Hutton, 2008; Munoz & Everling, 2004). Antisaccade trials typically have slower reaction times (RTs) and higher error rates (uninhibited saccades towards the stimulus; e.g., Brown, Goltz, Vilis, Ford, & Everling, 2006; Ethridge, Brahmbhatt, Gao, McDowell, & Clementz, 2009; Herweg et al., 2014; Pierce, McCardel, & McDowell, 2015; Pierce & McDowell, 2016b; Weiler & Heath, 2012), although task parameters and practice can modulate these antisaccade costs (Chiau et al., 2011; Smyrnis et al., 2002; Unsworth, Spillers, Brewer, & McMillan, 2011). Basic saccade circuitry activated during fMRI tasks has been thoroughly characterized in the literature and includes visual cortex, PPC, frontal and supplementary eye fields (FEF/SEF), thalamus, basal ganglia, and cerebellum; greater strength or extent of activation in these regions, and recruitment of additional cognitive control regions such as PFC and ACC, is observed during antisaccade tasks (Brown, Vilis, & Everling, 2007; Curtis & Connolly, 2008; Curtis & D'Esposito, 2003; Dyckman, Camchong, Clementz, & McDowell, 2007; Ford, Goltz, Brown, & Everling, 2005; Jamadar, Fielding, & Egan, 2013; McDowell, Dyckman, Austin, & Clementz, 2008; Reuter, Kaufmann, Bender, Pinkpank, & Kathmann, 2010).

Cognitive control of saccade tasks is dependent upon the context in which they are performed (Dyckman et al., 2007; Ethridge et al., 2009); one means of manipulating task context is by varying the proportion or probability of prosaccades and antisaccades within a mixed saccade block. As the probability of a given trial type decreases, its task set is less active and participants make more errors and have slower RTs (Chiau et al., 2011; Massen, 2004; Pierce & McDowell, 2016a). Alternately, a high probability of an antisaccade trial can slow down RTs of both trial types, presumably due to lingering motor inhibition (Barton, Greenzang, Hefter,

Edelman, & Manoach, 2006; Dorris, Pare, & Munoz, 2000; Pierce et al., 2015; Pierce & McDowell, 2016b). The current study explores the interaction between trial type probability and saccade task practice to investigate how increased experience with a challenging context can improve behavior.

Previous studies on practice of saccade tasks include a study (Dyckman & McDowell, 2005) that examined the behavioral effects of practicing antisaccades, prosaccades, or fixation for two weeks. All groups performed the tasks more quickly (faster RTs) after practice, while only individuals who practiced the antisaccade task had fewer antisaccade errors. Critically, those who practiced the prosaccade task produced more antisaccade errors at the end of the study, likely because the prosaccade task reinforced the visually-driven response that constitutes an error in the antisaccade task. In a similar study examining BOLD signal changes in a blocked design antisaccade task following a week of antisaccade, prosaccade, or fixation practice (Lee et al., 2013), only the antisaccade practice group demonstrated consistent decreases in saccade circuitry activation at post-test, despite a lack of significant changes in behavior. Furthermore, a recent study (Jamadar, Johnson, Clough, Egan, & Fielding, 2015) investigated practice of interleaved saccade trials using event-related BOLD fMRI. Participants performed mixed blocks of prosaccade and antisaccade trials in the scanner and then practiced a shortened version of the task daily for two weeks before a second fMRI session. Their results indicated a reduction in antisaccade RT with no change in error rate, and markedly increased BOLD signal across saccade circuitry for both trial types at the second time point. These studies offer conflicting evidence as to how saccade behavior and BOLD signal change with practice, but indicate that the activation of saccade circuitry can be modulated by task experience.

The present study combined practice of saccade tasks with a trial type probability manipulation to examine how both antisaccade and prosaccade trials in different task contexts were affected by either specific or general saccade practice. Participants completed an initial fMRI session with five blocks of varying probability of antisaccade to prosaccade trials (0, 25, 50, 75, or 100%) and then were divided into two practice groups for four days of saccade practice in the laboratory before an identical post-test fMRI session. Half of the participants were in the "specific" practice group – they practiced the same five mixed probability blocks each day that they performed during the fMRI testing sessions. The other half of participants were in the "general" group and practiced 5 blocks of 100% antisaccade trials. It was predicted that as the contexts of the saccade trials became more familiar over the course of the practice days, less cognitive control would be required to activate the appropriate task set. Thus, even in blocks with a low probability of a given trial type, the correct task set would be selected in a more automatic manner with less interference from the more probable task set.

Those who practiced the cognitive control components required by the specific probability blocks were expected to improve saccade behavior the most at post-test as a result of repeated exposure to all mixed contexts. In contrast, those who practiced general cognitive control with only antisaccade trials were expected to show less improvement in blocks with low antisaccade probability because they were not trained on conditions with frequent (or any) prosaccade trials. Prosaccade behavior was not expected to change significantly for either group. By comparing two practice groups, the different pattern of results observed in previous saccade practice studies may be clarified, as those studies administered only single or mixed saccade trial practice, but not both (Jamadar et al., 2015; Lee et al., 2013).

As participants in the current study became more familiar with the probability contexts and/or antisaccade task set, it was predicted that the need for effortful supervision by control processes would be reduced. Therefore, cognitive control regions associated with facilitating task rules and adapting to context, such as PFC and ACC, were expected to show a decrease in BOLD signal at post-test. Furthermore, participants who practiced the specific probability contexts were predicted to reduce activation in these cognitive control regions and saccade circuitry to a greater degree overall than the general antisaccade practice group. Their familiarity with the mixed contexts and expectation of the probability manipulation at post-test should have better prepared them for both trial types even in the low probability blocks. Overall, the increased exposure and extended training with saccade tasks should have allowed participants to better utilize contextual information and activate the appropriate task set more efficiently.

Methods

Participants

Sixty-five undergraduate students were recruited from the UGA Psychology Department online research pool and given course credit for their participation (as described in Pierce & McDowell, 2016b). Thirty-three individuals fulfilled exclusion criteria or voluntarily opted out before completing the study, leaving 32 right-handed participants who experienced no current major psychiatric disorders or substance abuse, had no metal implants, and had normal or corrected-to-normal vision (via self-report). Sixteen of the participants (mean age = 19 years; SD = 1; 5 males) were assigned to the general antisaccade practice group and sixteen (mean age = 20 years; SD = 5; 5 males) to the specific probability practice group (described below). All

participants provided written informed consent and activities were approved by the Institutional Review Board of the University of Georgia.

Task Design

Participants were presented with five rapid event-related saccade blocks with varying probability of occurrence of an antisaccade (AS) trial (relative to a prosaccade trial): 0, 25, 50, 75, and 100% AS. The blocks consisted of 60 saccade trials presented according to the overall probability, of which participants were not informed, (e.g., 25% AS block had 15 antisaccade and 45 prosaccade trials) interspersed with jittered fixation periods. All stimuli consisted of a 1° gray shape presented on a black background and central fixation appeared for 2000 to 8000 ms (average 3500 ms) between trials. For saccade trials, the trial type cue was illuminated around the cross for 500 ms (for prosaccades, a square; for antisaccades, a diamond). This was followed by a blank screen for 200 ms ("gap" presentation) and finally the peripheral stimulus at 5° or 10° right or left of the center for 800 ms. Two peripheral stimulus eccentricities were included to reduce the likelihood of participants' anticipating the response location and preparing a motor response in advance (data collapsed across amplitude for analyses). The practice tasks followed the same timing scheme as the fMRI scans, but were generated separately so that the exact trial timing and order differed between practice and MRI sessions; five unique 100% AS blocks were created for the general practice group.

Procedure

Participants attended an initial session where they completed demographic surveys and were screened for exclusion criteria. During this session, participants were introduced to the saccade paradigm by performing twenty mixed prosaccade ("look as quickly and accurately as possible towards the peripheral stimulus") and antisaccade ("look to the mirror image location of

the stimulus, same distance from the center") trials. During the subsequent MRI session, participants were positioned on the scanner table with the head secured. A high-resolution (T1-weighted) structural scan was obtained first for each participant, followed by the functional scans (T2*-weighted). Stimuli were displayed using Presentation software (Neurobehavioral Systems, Albany, CA) and a dual mirror system attached to the head coil that allowed the participant to view a projection screen at his/her feet and researchers to monitor the participant's eye. Right eye pupil position was sampled at 60 Hz (IView X MRI-LR system, SensoMotoric Instruments, Germany) and recorded for off-line analysis. Before beginning the saccade tasks, eye position was calibrated using IView's 5-point calibration and an in-house horizontal calibration.

After completing the baseline MRI, participants were assigned to one of two practice groups. Each group practiced five saccade blocks a day for four weekdays in the laboratory. The first group practiced the five "specific" probability blocks (0, 25, 50, 75, and 100% AS) in counterbalanced order across days. The second group practiced only "general" antisaccade blocks (100% AS). On the practice days, participants were seated in the laboratory with their head in a chin rest in front of the display monitor (Samsung 40-inch LCD) and the eye-tracking apparatus (EyeLink II, SR Research, Ontario, Canada) was placed on their head and adjusted. Eye position relative to the monitor was calibrated with both EyeLink's built-in 9-point calibration and an in-house horizontal 7-point calibration. Stimuli were displayed in a darkened room while the relative pupil positions of both eyes were sampled and digitized at 500 Hz. Following the four practice days, both groups completed a post-test fMRI session with the same scan order as at baseline.

Imaging Parameters

MR images were collected on a 3T GE Signa Excite HDx system (General Electric Medical Systems, Milwaukee, WI) at the University of Georgia Bio-Imaging Research Center. A high-resolution anatomical image was collected using a T1-weighted 3D FSPGR sequence (echo time (TE) = 3 ms, flip angle = 20°, field of view (FOV) = 240 mm x 240 mm, matrix size 256 x 256, 150 axial slices, in-slice resolution = 0.94 x 0.94 mm, slice thickness = 1.2 mm, scan time = 6 minutes 32 seconds). The functional scans were collected using a T2*-weighted gradient echo EPI sequence (TE = 30 ms, repetition time (TR) = 2000 ms, flip angle = 90°, FOV = 220 mm x 220 mm, matrix size = 64 x 64, 33 interleaved oblique slices aligned with the AC-PC plane, in-slice resolution = 3.4 x 3.4 mm, slice thickness = 4 mm, slice gap = 0 mm, and 4 dummy volumes for magnet stabilization, 158 volumes, scan time = 5 minutes 24 seconds).

Analyses

Eye position data were analyzed using custom scripts written in MATLAB (MathWorks, Natick, MA). Trials were manually scored for initial direction of response (eye movements with velocities surpassing 20°/sec were classified as saccades) and correct response RT. Error rate was defined as the number of trials with an initial saccade in the incorrect direction out of the total number of analyzable trials; RT was defined as the time from the appearance of the peripheral circle to the initiation of the first saccade. Trials with no response, blinks at stimulus onset, anticipatory saccades (faster than 90 ms RT or during the gap window), or with insufficient data quality due to loss of pupil tracking were excluded from further analyses. Out of 150 trials per condition, an average of 137 (baseline)/ 130 (post-test) antisaccade trials and 138 (baseline)/ 132 (post-test) prosaccade trials were included in the analysis. Statistical analyses on eye movement metrics were performed using SAS Version 5.1 (SAS Institute Inc., Cary, NC)

and SPSS Version 22 (IBM Corp., Armonk, NY) software packages. To quantify the effects of practice on saccade behavior, a 2x2x4 (practice group (specific/general) by time point (baseline/post-test) by probability block) ANOVA was performed on error rate and correct trial RT at baseline and post-test scans. For antisaccade trials the levels of probability were 25, 50, 75, and 100% AS and for prosaccade trials they were 0, 25, 50, and 75% AS.

Functional MRI data were analyzed using the AFNI software package (Cox, 1996, 2012) with initial processing steps including: slice-timing correction, volume alignment to account for subject motion, resampling to 4 mm^3 voxel grid, spatial standardization to a Talairach template, spatial smoothing (4 mm full width-half maximum Gaussian kernel), and voxel-wise scaling to a mean of 100. Based on each participant's behavioral responses, a general linear model was fit with stimulus regressors for correct antisaccades, error antisaccades, correct prosaccades, and error prosaccades. Regressors of no interest were also included for baseline drift (linear, quadratic, cubic) and rotational movement in the x, y, and z planes. Coefficients for correct trials then were entered into a 2x2x4 (practice group (specific/general) by time point (baseline/post-test) by probability block) ANOVA for antisaccade and prosaccade trials separately. For antisaccade trials the levels of probability were 25, 50, 75, and 100% AS and for prosaccade trials they were 0, 25, 50, and 75% AS. The group analyses were confined to regions within a custom brain mask created from the average gray matter segmentation from all subjects' anatomical images using FSL's FAST (FMRIB Software Libraries Automated Segmentation Tool; Zhang, Brady, & Smith, 2001) in conjunction with putamen, caudate, and thalamus regions as defined by AFNI's Talairach-Tournoux atlas (Talairach & Tournoux, 1988). To protect against false positives resulting from multiple comparisons across voxels, a clustering method

derived from Monte Carlo simulations was applied to the group maps (AFNI's 3dclustsim). With a voxel-wise $p<.01$ a family-wise $\alpha<.05$ was preserved by clusters with a minimum of 23 voxels.

Results

Behavioral Responses

The ANOVA on antisaccade behavior indicated a significant effect of time point on both antisaccade error rate ($F(1,30)=5.7$, $p<.05$, $\eta^2=.16$) and correct RT ($F(1,30)=14.7$, $p<.01$, $\eta^2=.33$). There were fewer errors and faster RTs at post-test than baseline (Table 4.1). There was also a significant main effect of probability for both measures (error rate: $F(3,90)=4.6$, $p<.01$, $\eta^2=.13$; RT: $F(3,90)=6.7$, $p<.001$, $\eta^2=.19$) and a significant time point by probability interaction for RT ($F(3,90)=5.4$, $p<.01$, $\eta^2=.15$). Blocks with a higher antisaccade probability had fewer errors and slower RTs, with this pattern being most dominant at baseline. There were no significant main or interaction effects involving practice group.

The ANOVA on prosaccade behavior showed a significant effect of probability on correct RT ($F(3,90)=7.0$, $p<.001$, $\eta^2=.19$). Blocks with a higher prosaccade probability had faster RTs. There was an interaction between time point and practice group on error rate ($F(1,30)=6.6$, $p<.05$, $\eta^2=.18$), with the general practice group committing more prosaccade errors at post-test, although average prosaccade error rates were always less than 5% of trials. No other effects reached statistical significance.

BOLD Signal Changes

Main Effect of Time Point

For antisaccade trials, the practice group by time point by probability ANOVA revealed a main effect of time point in seven clusters that included the canonical saccade circuitry (Figure

4.1/Table 4.2). For prosaccade trials, there was a main effect of time point in six clusters, many of which were located in similar regions as the antisaccade trial clusters (Table 4.3). All clusters showed decreased BOLD signal from baseline to post-test. Notably, bilateral PFC showed a positive signal for antisaccade trials at baseline, but no signal at post-test; the bilateral parietal/temporal clusters showed the same pattern for prosaccade trials. The change in BOLD signal from baseline to post-test for antisaccade trials did not correlate with the change in antisaccade RT in any of these regions. For prosaccade trials, most regions (except the bilateral cuneus cluster which was marginal, p=.07) showed a negative correlation between BOLD signal change and RT change from baseline to post-test, such that individuals who had slower prosaccade RTs at post-test than baseline showed the greatest decrease in BOLD signal. For example, Figure 2 shows the relationship between prosaccade activation in the left parietal/temporal/cingulate region and RT (r=-0.18, p<.05), implying that the BOLD signal decreases were not due simply to shortened neural processing time.

Main Effect of Trial Type Probability

For antisaccade trials, the main effect of probability resulted in eight clusters (Figure 4.3/Table 4.2) that showed two general patterns. The first pattern observed in left precuneus, ACC, and right MFG showed the highest BOLD signal in the block with the fewest antisaccades (25% AS) and the lowest BOLD signal in the block with the most antisaccades (100% AS). The second pattern observed in right and left middle occipital gyrus (MOG), left angular gyrus, left MFG, and left precentral gyrus showed weak or negative activation for the block with the fewest antisaccades (25% AS) and positive or no signal change for the other blocks. For prosaccade trials, a similar effect of probability as the first pattern described for antisaccades was observed in nine clusters (Figure 4.3/Table 4.3), with the direction of responses reversed relative to

antisaccade trials due to the reversed prosaccade trial type probability (i.e., high antisaccade probability means low prosaccade probability). These regions thus showed the highest BOLD signal in the block with the fewest prosaccades (75% AS) and the lowest BOLD signal in blocks with the most prosaccades (0% and 25% AS).

Main Effect of Practice Group

The main effect of practice group did not yield any significant clusters for antisaccade trials. For prosaccade trials, the effect of practice group showed two significant clusters in right MFG and left cerebellum (Table 4.3). These regions had greater BOLD signal for those in the general practice group than the specific practice group.

Practice Group by Time Point Interaction

The interaction between practice group and time point resulted in six significant clusters for antisaccade trials and two clusters for prosaccade trials (Figure 4.4/Tables 4.2 and 4.3). Across regions and trial types, the specific practice group showed a strong decrease in activation from baseline to post-test. In contrast, the general practice group showed either no change or a slight increase in BOLD signal over time.

Other Interactions

For antisaccade trials, the interaction between practice group and antisaccade probability resulted in one small cluster in posterior cingulate (Table 4.2). This region showed greater BOLD signal for the general practice group in the block with the fewest antisaccades (25% AS), greater BOLD signal for the specific practice group in the block with all antisaccades (100% AS) and little difference between groups in the other blocks (50% and 75% AS). Antisaccade trials also resulted in a time point by probability interaction in two clusters in cingulate and right precuneus. These regions had strong BOLD signal in the all-antisaccade block (100% AS) and

weak signal in the low probability antisaccade block (25% AS) at baseline, with the opposite pattern at post-test. Prosaccade trials did not show any other two-way interactions. Neither antisaccade nor prosaccade trials showed a significant three-way interaction between practice group, time point, and probability.

Discussion

Cognitive control is recruited according to current goals to facilitate performance of a novel task set in an unfamiliar context, yet with practice the task set can be strengthened and executed with fewer demands for top-down supervision. In this study the effects of specific and general saccade task practice on performance of blocks with varying trial type probability were investigated in healthy young adults using BOLD fMRI. The specific group practiced the same five mixed probability blocks as assessed during testing and the general group practiced only an all-antisaccade block. Analysis of fMRI brain activation indicated that the specific practice group decreased BOLD signal strongly from baseline to post-test in several regions, while the general practice group showed little change in those regions. Additionally, widespread decreases in BOLD signal were observed for all participants across saccade circuitry for both trial types following practice.

Behavioral results demonstrated that regardless of whether a participant practiced the specific mixed probability task or the general antisaccade task, both antisaccade error rate and RT decreased at post-test while prosaccade behavior changed minimally. Consistent with previous reports (Massen, 2004; Pierce & McDowell, 2016a, 2016b), an effect of probability was observed in antisaccade error rate and RT as well as prosaccade RT: blocks with a high probability of antisaccade trials had lower antisaccade error rate and slower RTs for both trial

types. Taken together, these results suggest that while both types of saccade practice were effective at improving behavior and generally reducing activation in saccade circuitry, the specific practice group's more extensive exposure to the probability contexts allowed them to create more efficient task representations that led to reduced BOLD signal in additional brain regions at post-test than the general practice group. Therefore, training on a difficult task in isolation is not as effective at reducing the demand for cognitive control as practicing the task within a mixed context.

Reduced BOLD Signal following Saccade Practice

In the comparison between baseline and post-test fMRI scans for both antisaccade and prosaccade trials, widespread saccade circuitry showed a reduction in BOLD signal strength. Antisaccade trials showed more extensive significant decreases than for prosaccade trials, with decreases in bilateral PPC (precuneus, inferior parietal lobule), cuneus, FEF/SEF, insula, ACC, and bilateral PFC. The PFC clusters, in particular, showed a positive BOLD signal at baseline and no signal at post-test for antisaccade trials. This supports the notion of a "scaffolding" cognitive control system for learning novel stimulus-response mappings (Chein & Schneider, 2005; Kelly & Garavan, 2005). The antisaccade response (look to the mirror image location) requires an unfamiliar transformation of visual stimulus information and engages PFC (and other regions) to facilitate a volitional saccade over a visually-driven response. With practice, this mapping is strengthened and less top-down control is required to correctly execute the necessary inversion. For prosaccade trials, a decrease also was observed in parietal cortex, extending into left post/precentral gyrus (FEF) and cingulate/SEF, as well as in the cuneus. In these core saccade visual-motor regions, decreased BOLD signal at post-test may be due to increased network efficiency and strengthened, distributed task set representations. Since the current study

included only groups with active task practice, another consideration is that some changes in activation may have been caused by test-retest effects or because participants were more comfortable with the MRI/eye tracking environment in general and not because of saccade task practice *per se*.

The pattern of behavioral changes, however, demonstrates that saccade practice was effective at improving antisaccade error rates and reducing antisaccade RTs for both groups at post-test, while diminishing the difference among probability blocks as measured at baseline. This is broadly consistent with previous saccade practice studies: Dyckman & McDowell (2005) reported fewer antisaccade errors for those who practiced antisaccades and faster antisaccade RTs overall; Jamadar et al. (2015) reported faster RTs for both antisaccades and prosaccades after mixed saccade practice, although no change in antisaccade error rate. The error rates in that study, however, were lower (~10%) than those reported here (~20%) and participants may have approached peak performance during the baseline session. Interestingly, in the current results individual change in antisaccade RT following practice did not correlate with changes in antisaccade BOLD signal, but prosaccade RT change did negatively correlate with prosaccade BOLD signal change. Participants who reduced their RT with practice thus were not driving BOLD signal changes simply due to shorter neural processing time (D'Esposito et al., 1997; Poldrack, 2000). Indeed, those who had the largest increase in prosaccade RT showed the greatest reduction in BOLD signal, perhaps indicating that better network efficiency was achieved overall by weakening the initial influence of the visual stimulus on motor output.

Effects of Trial Type Probability

The analysis of trial type probability revealed effects in posterior temporal/occipital, parietal and frontal regions for both trial types. In most of these clusters, both trial types showed

the greatest BOLD signal in blocks with a low probability of that trial type and the least signal in blocks with a high trial type probability. This pattern suggests that when a trial type was unexpected its task set was poorly activated and greater effort or attention (and therefore a stronger BOLD signal) was required to correctly execute the saccade. In Pierce & McDowell (2016b), we reported trial type probability effects from these subjects at baseline, focusing only on the three mixed blocks (25, 50, and 75% AS). In that analysis strong probability effects were observed for prosaccade trials, with activation in the low prosaccade probability block (75% AS) reaching antisaccade levels in precuneus, occipital/temporal cortex, medial frontal gyrus, and right MFG (Pierce & McDowell, 2016b). With the inclusion of the single trial type blocks and post-test data in the current analysis, probability effects for antisaccade trials were detected in similar regions. Thus with a broader range of probabilities and more trials, complex antisaccade trials showed sensitivity to context as well as basic prosaccade trials.

There also were interactions of trial type probability with time point and with practice group for antisaccade trials. The interaction with time point indicated that at post-test clusters in parietal cortex showed an increase in BOLD signal for the low antisaccade probability block and a decrease for the all-antisaccade block. Participants' knowledge at post-test of the probability manipulation (due to their initial exposure or daily task practice) may have reduced demands for visual attention and spatial transformation processes during blocks with greater likelihood of an antisaccade trial. The interaction between probability and practice group resulted in a small cluster in posterior cingulate with greater activation for the general practice group in the low antisaccade probability block and weaker activation in the all-antisaccade block. This may reflect differences in visual processing based on the practice groups' differing exposure to each probability block.

Specific versus General Saccade Task Practice

While the main effect of time point highlighted many regions that showed decreased BOLD signal following practice for all participants, the practice group by time point interaction identified clusters in which the groups showed divergent responses. The specific practice group showed a clear decrease in all of these regions (including insula/superior temporal gyrus, right precentral gyrus and ACC) over time, while the general practice group showed no change or a small increase in BOLD signal. This pattern implies that the specific practice group's greater experience with the different probability blocks allowed them to reduce demand for the cognitive control and attention processes required to select the appropriate task set for both trial types (Bassett, et al., 2015). As with the main effect of time point, antisaccade trials showed more extensive regions of significance, while prosaccade trials showed a similar direction of effect in more circumscribed clusters. The insula, in particular, showed a marked effect for antisaccade trials and has been shown previously to be activated in response to the greater cognitive and motor demands of a novel antisaccade task (Jamadar, et al., 2013). The ACC also showed this same pattern and has been related to conflict monitoring during task performance and signaling that greater cognitive control should be exerted by PFC (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Braver, Barch, Gray, Molfese, & Snyder, 2001; Carter & van Veen, 2007; MacDonald, Cohen, Stenger, & Carter, 2000). Thus for the specific practice group, more familiarity with the probability contexts at post-test may have diminished the effective conflict on low probability and antisaccade trials and the need for ACC recruitment.

The lack of signal reduction in ACC for the general practice group, however, suggests that trial conflict was not reduced to the same degree by practice of the challenging antisaccade task by itself. This kind of single trial type practice presumably did not account for the additional

task switching or working memory demands in the mixed saccade blocks (cf. contextual interference in motor training; Lage et al., 2015; Magill & Hall, 1990). The unexpected occurrence of a low probability trial type and the need to switch task sets in these blocks evidently engaged some task selection processes at least as much at post-test as during the baseline scan. This limited familiarity and the stronger attentional demands associated with it may account for the fact that the general practice group showed greater activation overall for prosaccade trials in right MFG and left cerebellum. Together these effects suggest that the specific practice group was able to more thoroughly strengthen task set and context representations, increase saccade circuitry efficiency, and reduce the demand for cognitive control, in spite of behavioral improvements being observed for both groups.

Conclusions

This study investigated the impact of specific versus general saccade practice on behavior and BOLD signal activation in a mixed saccade task. The task included blocks of randomly interleaved antisaccade and prosaccade trials with varying trial type probability. Both antisaccade error rate and RT decreased following practice, as did the BOLD signal across saccade circuitry for both trial types. Cognitive control regions such as PFC, ACC, and PPC showed positive activation at baseline for antisaccade trials that then diminished or disappeared at post-test as the novel task set was strengthened and could be executed in a more automated manner. The trial type probability manipulation led to increased activation for low probability trials in visual and motor pathways, with similar effects for both simple and complex trial types. Finally, the practice groups showed opposing changes over time in several regions, with the specific practice group decreasing BOLD signal at post-test and the general practice group changing little. This likely resulted from the increased familiarity with the different probability

contexts that the specific practice group gained. Greater exposure to a mixed context afforded additional training with switching and maintaining both task sets in a single block, whereas general practice reinforced a single mode of responding that was not as beneficial in the mixed contexts. These findings generally demonstrate that with practice of a complex task in varying contexts, participants can learn and strengthen new task sets and reduce demand for cognitive control supervision of task performance.

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	Error Rate (%)		RT (ms)	
	Baseline	Post-test	Baseline	Post-test
Antisaccades				
25% AS	26.4 (18.6)	18.0 (18.1)	266 (42)	257 (41)
50% AS	27.2 (14.7)	20.2 (14.9)	273 (42)	256 (44)
75% AS	23.2 (13.5)	17.7 (12.4)	283 (42)	258 (48)
100% AS	18.4 (13.7)	17.0 (11.7)	290 (40)	257 (49)
Prosaccades				
0% AS	2.0 (2.2)	2.1 (2.7)	191 (23)	188 (20)
25% AS	3.1 (4.4)	3.9 (4.6)	192 (23)	191 (23)
50% AS	3.5 (4.0)	3.7 (5.3)	201 (27)	194 (23)
75% AS	2.2 (5.1)	4.1 (5.4)	199 (30)	197 (26)

Table 4.1 Error rate and correct reaction time at baseline and post-test MRI sessions for all participants. Values are given as mean (SD).

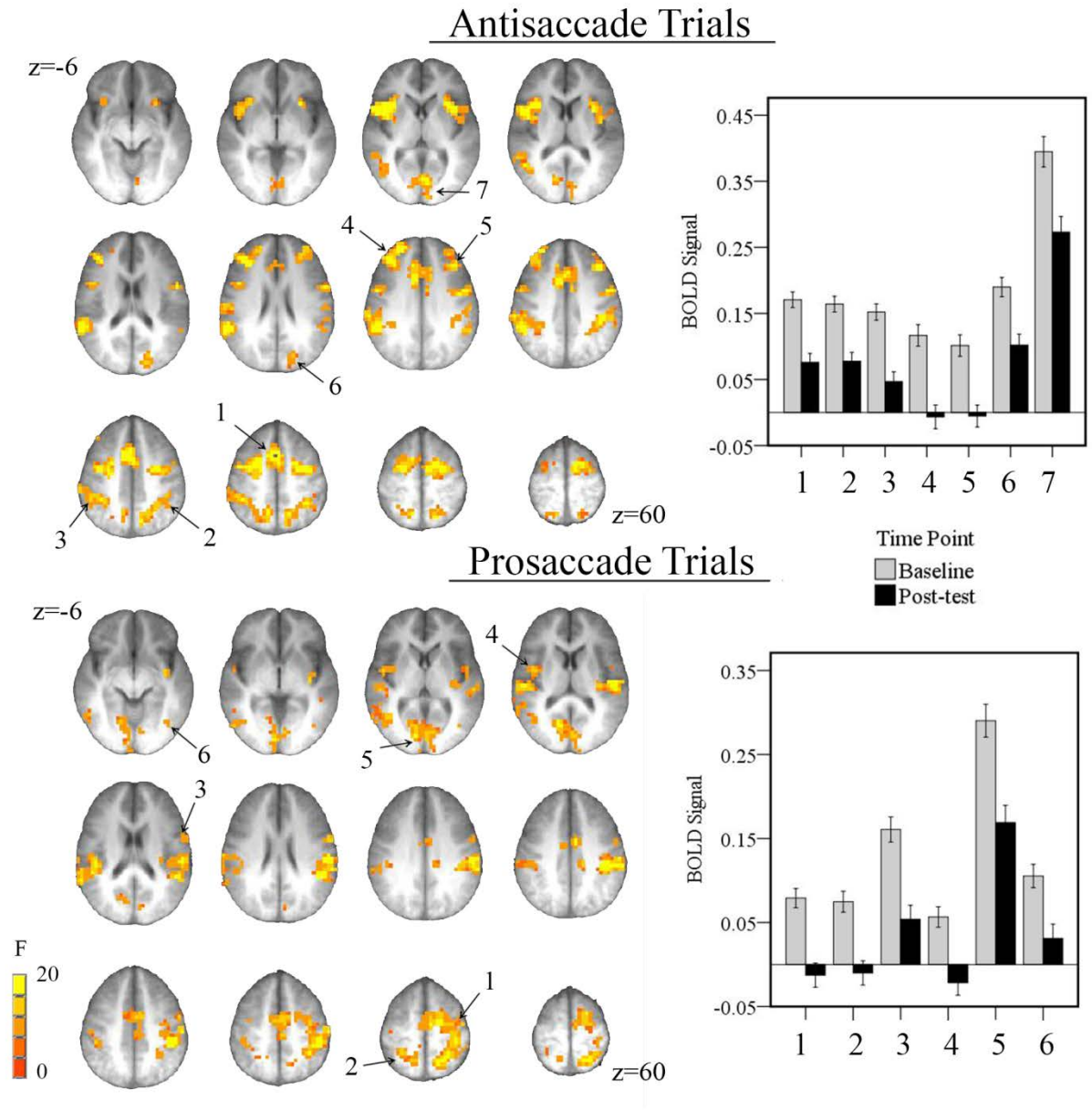

Figure 4.1 Main effect of time point. *Left*: Maps of the time point main effect for antisaccade and prosaccade trials; brighter colors represent higher *F*-values. Antisaccade trials resulted in significant clusters in: 1) bilateral FEF/SEF/ACC/ bilateral insula, 2) left inferior parietal lobule/precuneus, 3) right inferior parietal lobule/precuneus, 4) right middle/superior frontal gyrus, 5) left middle/superior frontal gyrus, 6) left cuneus, and 7) left lingual gyrus. Prosaccade trials resulted in significant clusters in: 1) left inferior parietal lobule/superior temporal

gyrus/cingulate, 2) right inferior parietal lobule/superior temporal gyrus, 3) left precentral gyrus, 4) right insula, 5) bilateral cuneus, and 6) left middle occipital gyrus. Brain images are displayed in radiological convention with functional results (voxel-wise $p<.01$, family-wise $\alpha<.05$) overlaid on the average of the standardized anatomical images from all subjects. *Right*: plots of the BOLD signal from all regions for each trial type showing decreased activation from baseline to post-test scans. Details of the clusters are provided in Tables 4.2 and 4.3.

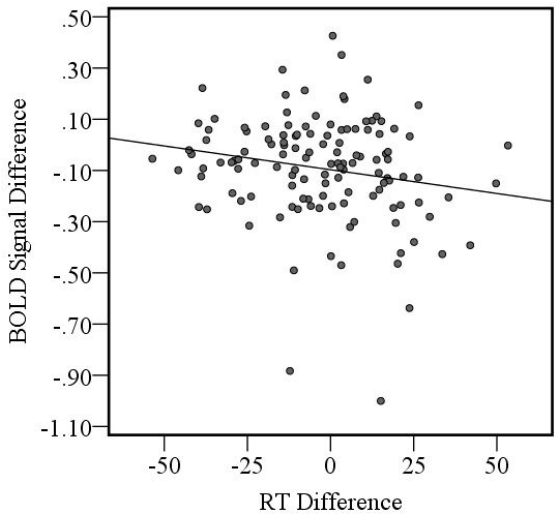

Figure 4.2 Correlation between prosaccade RT and BOLD signal difference (post-test minus baseline). The BOLD signal was extracted from the cluster including left parietal and temporal regions (labelled 1 in Fig. 4.1). Negative values indicate a reduction in BOLD signal or faster RTs following practice and data points represent individual participants in each of the four probability blocks. Participants who had slower RTs at post-test had the greatest reduction in BOLD signal. A similar relationship was observed with each of the six clusters in the prosaccade time main effect; antisaccade trials showed no such correlation.

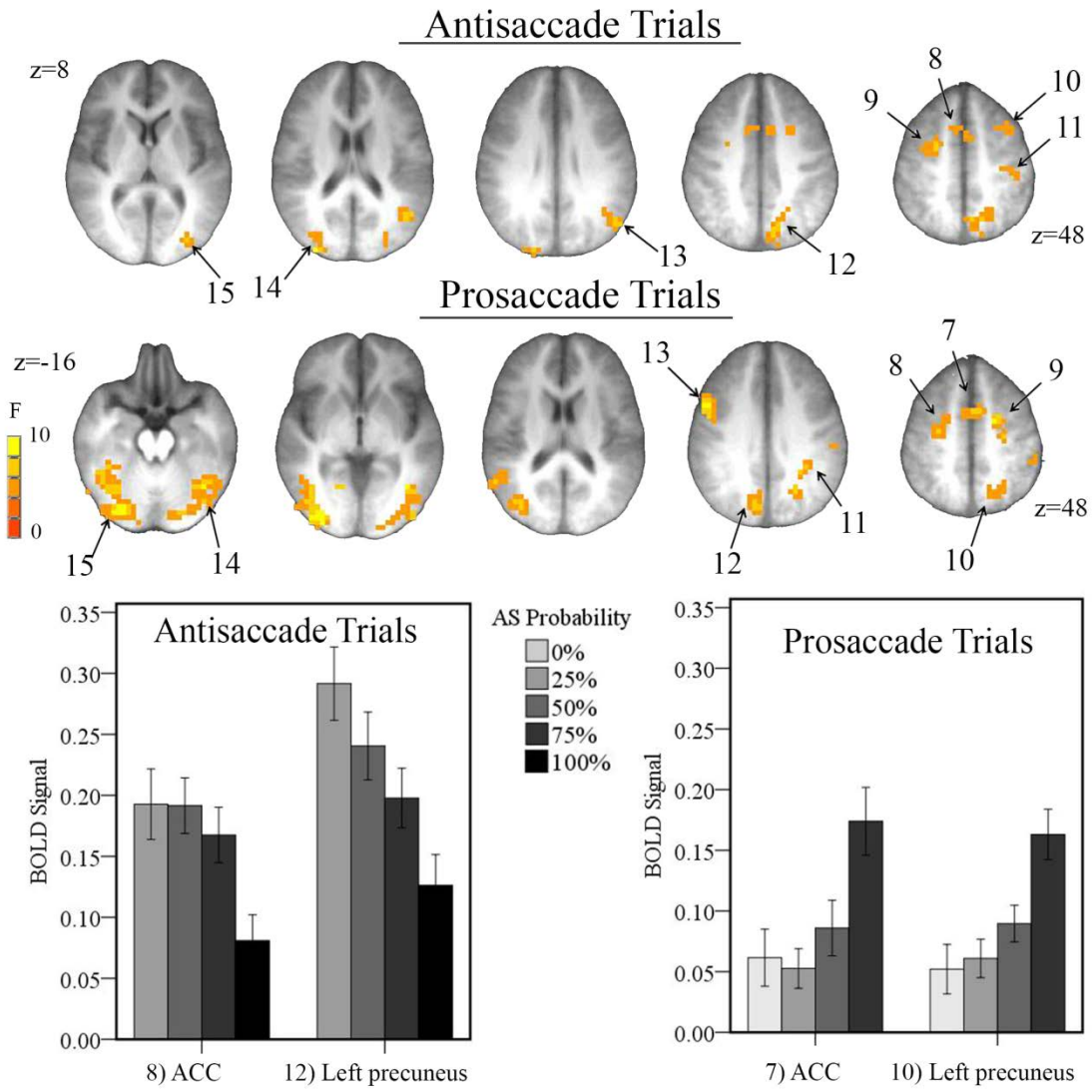

Figure 4.3 Main effect of trial type probability. *Top*: Maps of the probability main effect for antisaccade and prosaccade trials; brighter colors represent higher *F*-values. Antisaccade trials resulted in significant clusters in: 8) ACC, 9) right middle frontal gyrus, 10) left middle frontal gyrus, 11) left pre/postcentral gyrus, 12) left precuneus, 13) left middle/superior temporal gyrus, 14) right middle occipital gyrus, and 15) left middle occipital gyrus. Prosaccade trials resulted in significant clusters in: 7) ACC, 8) right middle/medial frontal gyrus, 9) left middle/medial frontal gyrus, 10) left precuneus, 11) left inferior parietal lobule, 12) right precuneus, 13) right inferior/middle frontal gyrus, 14) left middle occipital gyrus, and 15) right middle occipital

gyrus. Brain images are displayed in radiological convention with functional results (voxel-wise $p<.01$, family-wise $\alpha<.05$) overlaid on the average of the standardized anatomical images from all subjects. *Bottom left*: plots of the BOLD signal from antisaccade trials in two cognitive control regions; in ACC and left precuneus activation was the highest in the low antisaccade probability blocks (25% and 50% AS) and lowest in the all-antisaccade block (100% AS). *Bottom right*: plots of BOLD signal from prosaccade trials in two prosaccade clusters similar to those locations shown for antisaccade trials; prosaccade activation showed a comparable response to probability with the strongest BOLD signal in the low prosaccade probability block (75% AS). Details of all clusters are provided in Tables 4.2 and 4.3.

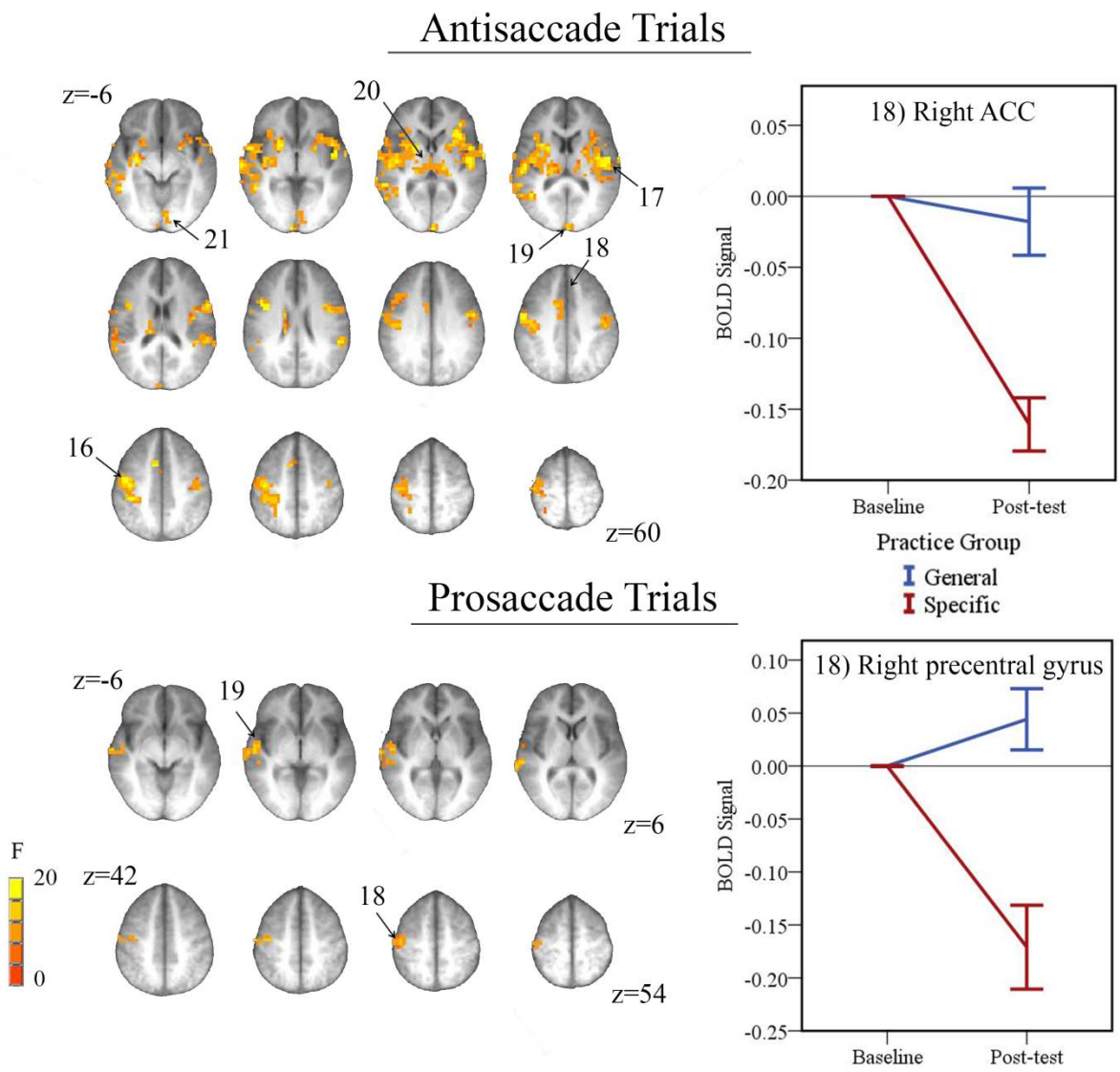

Figure 4.4 Practice group by time point interaction. *Left*: Maps of the practice group by time point interaction for antisaccade and prosaccade trials; brighter colors represent higher *F*-values. Antisaccade trials resulted in significant clusters in: 16) right precentral/superior temporal gyrus, 17) left precentral/superior temporal gyrus, 18) right ACC, 19) thalamus, 20) left cuneus, and 21) left lingual gyrus. Prosaccade trials resulted in significant clusters in: 18) right superior/middle temporal gyrus and 19) right post/precentral gyrus. Brain images are displayed in radiological convention with functional results (voxel-wise $p<.01$, family-wise $\alpha<.05$) overlaid on the average of the standardized anatomical images from all subjects. *Top right*: plot of the BOLD signal from

antisaccade trials adjusted for baseline values in the right ACC cluster (all regions showed a similar pattern) indicating that the specific practice group decreased activation from baseline to post-test while the general practice group did not change. *Bottom right*: plot of BOLD signal from prosaccade trials in the right precentral gyrus showing a similar effect with a slight increase at post-test for the general practice group. Details of all clusters are provided in Tables 4.2 and 4.3.

Antisaccade Anatomical Region	Peak F-value	X	Y	Z	Size (voxels)
Time Point Effect					
1) Bilateral FEF, SEF, anterior cingulate, bilateral insula	44.3	46	7	8	793
2) Left inferior parietal, precuneus	29.2	-14	-61	52	216
3) Right inferior parietal, precuneus	30.2	54	-41	20	365
4) Right middle/superior frontal gyrus	37.3	22	47	32	127
5) Left middle/superior frontal gyrus	25.2	-34	27	32	76
6) Left cuneus, precuneus	13.6	-14	-81	20	30
7) Left cuneus, lingual gyrus	19.0	-6	-69	8	79
Probability Effect					
8) Anterior cingulate/ medial frontal gyrus	5.7	6	11	40	23
9) Right middle frontal gyrus	6.6	22	-1	44	30
10) Left middle frontal gyrus	5.8	-26	11	44	25
11) Left pre/postcentral gyrus	6.4	-30	-25	64	23
12) Left precuneus, cuneus	7.6	-14	-69	40	67
13) Left middle/superior temporal, angular gyrus	7.3	-42	-57	20	41
14) Right cuneus, middle occipital gyrus	8.4	30	-85	20	32
15) Left middle occipital gyrus	6.7	-30	-77	8	26
Group by Time Point Interaction					
16) Right precentral gyrus, superior temporal gyrus, insula	25.1	38	7	24	733
17) Left precentral gyrus, superior temporal gyrus, insula	27.3	-46	-13	8	439
18) Right anterior cingulate, medial frontal gyrus	19.8	10	7	44	40
19) Bilateral thalamus	19.5	18	-13	16	79
20) Left cuneus	17.4	-2	-93	8	24
21) Left lingual gyrus, declive	14.4	-6	-77	-4	31
Group by Probability Interaction					
22) Left posterior cingulate, culmen	9.9	-6	-41	8	23
Time Point by Probability Interaction					
23) Bilateral cingulate, precuneus	7.8	6	-41	40	44
24) Right precuneus	11.0	14	-69	36	26

Table 4.2 Description of the significant clusters for antisaccade trials in the time point by probability by practice group ANOVA. Coordinates refer to the Talairach-Tournoux atlas and voxel size is based on 4 mm^3 voxels.

Prosaccade Anatomical Region	Peak F-value	X	Y	Z	Size (voxels)
Time Point Effect					
1) Left inferior parietal lobule, postcentral gyrus, insula, superior temporal gyrus, cingulate	35.6	-38	-33	40	749
2) Right inferior parietal lobule, postcentral gyrus, superior temporal gyrus	19.8	42	-25	16	320
3) Left precentral gyrus	15.2	-58	-1	24	30
4) Right insula	17.8	50	-5	4	39
5) Bilateral cuneus, lingual gyrus, right fusiform gyrus	19.8	14	-65	12	214
6) Left fusiform, middle occipital gyrus	16.4	-38	-65	4	28
Probability Effect					
7) Bilateral anterior cingulate, medial frontal gyrus	6.4	-6	3	48	24
8) Right middle/medial frontal gyrus, precentral gyrus	6.2	26	-13	47	38
9) Left middle/medial frontal gyrus, precentral gyrus	9.2	-18	-5	48	70
10) Left precuneus, superior parietal lobule	10.5	-22	-57	28	58
11) Left inferior parietal lobule, postcentral gyrus	7.5	-30	-41	32	41
12) Right precuneus, cuneus	8.3	14	-65	28	49
13) Right inferior/middle frontal gyrus, precentral gyrus	8.1	46	7	32	55
14) Left fusiform gyrus, middle occipital gyrus, declive	12.1	-38	-53	-4	249
15) Right fusiform gyrus, middle occipital gyrus, declive	12.3	26	-77	-12	428
Group Effect					
16) Right middle frontal gyrus	16.1	38	23	44	27
17) Left cerebellum	11.2	-34	-69	-32	24
Group by Time Point Interaction					
18) Right superior/middle temporal gyrus	15.5	50	-9	0	58
19) Right post/precentral gyrus	14.1	42	-21	52	34

Table 4.3 Description of the significant clusters for prosaccade trials in the time point by probability by practice group ANOVA. Coordinates refer to the Talairach-Tournoux atlas and voxel size is based on 4 mm^3 voxels.

CHAPTER 5

DISCUSSION

Cognitive control provides top-down supervision of sensory and motor processes to adapt behavior flexibly to current goals. A critical aspect of this adaptive mechanism is the ability to respond to changing contexts in order to optimize an individual's response strategy based on salient sensory input and recent experience. When the contingencies of the environment shift, the brain must be able to recognize these changes and appropriately facilitate task selection processes. By utilizing trial history (ir)regularities to learn and bias task sets, cognitive control ensures individuals the greatest likelihood of successful behavior across a range of contexts that may be encountered in daily life.

In the three studies presented in Chapters 2-4, the impact of context on cognitive control was examined in simple and complex saccade tasks. The study in Chapter 2 demonstrated how a regular trial structure encouraged sustained cognitive control activation across trials, whereas an unpredictable trial structure with frequent task switching engaged cognitive control transiently during high conflict trials. The study presented in Chapter 3 manipulated the relative probability of antisaccade and prosaccade trial types and revealed a greater cost of low trial type probability for the simple prosaccade task. Finally, the study in Chapter 4 investigated how performance changed after individuals learned the novel antisaccade task set or mixed probability contexts during a week of saccade practice. Both groups demonstrated antisaccade behavioral improvements and decreased BOLD signal across canonical saccade circuitry following practice. The specific practice group, however, showed strong reductions in BOLD signal in additional

regions, while the general practice group showed little signal change in the these regions over time. Together these studies highlight contextual factors which challenge cognitive control neural systems, with or without corresponding behavioral costs, and illustrate the flexible nature of cognitive control mechanisms during simple and complex visual-motor tasks.

ACC and Conflict Monitoring

Over the past several decades, neuroimaging has greatly advanced the understanding of brain function by identifying activation in specific brain regions associated with various cognitive, sensory, and motor tasks. In cognitive control paradigms, findings from a number of fMRI studies supported lesion research (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Pierrot-Deseilligny, Muri, Nyffeler, & Milea, 2005) indicating a central role for prefrontal cortex (PFC) during processes such as working memory, inhibition, and selective attention (e.g., Aron, Robbins, & Poldrack; 2014; Banich et al., 2000; Duncan, 2001; Koechlin, Ody, & Kouneiher, 2003; Miller & Cohen, 2001). Further research suggested a complementary role for medial frontal and anterior cingulate cortex (ACC), although the exact nature of the functional relationship between these regions, cognitive control, and task performance remained equivocal (Gaymard et al., 1998; Glascher et al., 2012; MacDonald et al., 2000). Seminal work by Carter and colleagues (Botvinick et al, 2001; Carter et al., 1998) posited a conflict monitoring hypothesis in which the ACC detected multiple types of conflict in incoming neural signals from across the brain and directed PFC to increase facilitation of goal-related processes in order to disambiguate the signals, resolve the conflict, and perform the correct behavior.

While the veracity and specificity of this hypothesis remains open to debate (Badre, 2004; Carter & van Veen, 2007; Milham & Banich, 2005; Shenhav et al., 2013), ACC activation

undoubtedly is observed during cognitive control tasks when conflicting stimulus-response mappings are engaged simultaneously, such as during an antisaccade task (Brown, Vilis, & Everling, 2007; Jamadar et al., 2013; Ford et al., 2005; McDowell et al., 2008). The current set of studies investigated the ACC's response to contextual changes that biased the conflict between antisaccade and prosaccade task sets. In Chapter 2, antisaccade and prosaccade trials were performed in two mixed contexts with contrasting structures. One context consisted of alternating blocks of fixation, prosaccade trials, and antisaccade trials, where participants performed the same trial type repeatedly and in a predictable order. The other context consisted of pseudo-randomly interleaved prosaccade and antisaccade trials interspersed with fixations of varying length. In the latter context, participants frequently had to switch between the two saccade task sets in an unpredictable order. As expected, the high conflict between the two task sets in the interleaved context resulted in greater BOLD signal in a number of regions including ACC. The blocked context had weak activation in ACC for both trial types, indicating that the repeated performance of a single trial type did not trigger the conflict monitoring system. Right PFC, however, did show a positive signal for both saccade types in the blocked context, implying that cognitive control was sustained throughout the paradigm to maintain both task sets, although the lack of trial-to-trial variation in task demands and task set conflict did not require ACC to signal any cognitive control adjustments to PFC.

Within the interleaved context, the ACC responded most strongly for antisaccade trials and trials that required switching task sets from the previous trial. This is consistent with the main effect of trial type in Chapter 3 and earlier studies indicating that novel antisaccade trials require higher levels of cognitive control than prosaccade trials (Hutton, 2008; McDowell et al., 2008). In addition, task switching studies from various cognitive domains have shown that the

ACC, PFC, and PPC are activated during task switch trials to support the maintenance and reconfiguration of multiple task sets (Dove et al., 2000; Johnston et al, 2007; Liston et al., 2006). It is not surprising, therefore, that the trials during which a participant had to perform the complex antisaccade response and execute a task switch resulted in the strongest BOLD signal in ACC. The bias towards the habitual prosaccade response was increased after completing a prosaccade trial such that a subsequent antisaccade trial required additional facilitation by the cognitive control network. Indeed, the behavioral results demonstrated that this antisaccade task switch often failed to be completed and participants erroneously looked towards the peripheral stimulus on about a third of the trials. These frequent errors may have contributed to the recruitment of the ACC throughout the task (Ford et al., 2005; Polli et al., 2005) if conflict arose due to the difference between the instructed goal and actual behavior. During the correct antisaccade switch trials, however, the observed increases in ACC activation evidently reflected a successful engagement of cognitive control and reconfiguration of the ocular motor task set.

Differential ACC activation was observed not only in Chapter 2 when comparing task structures, but also in Chapter 4 in blocks with variable trial type probability (see next section) and following saccade practice, especially for antisaccade trials. Greater BOLD signal was measured at the baseline scans when participants were unfamiliar with the task sets and probability contexts and conflict between the competing motor responses was high. In the resulting statistical maps, the clusters which encompassed the ACC often extended into medial frontal gyrus, pre-supplementary motor area, and/or SEF. These latter regions are related to motor planning and volitional saccade generation, and typically are activated during antisaccade trials (Jamadar et al., 2013; McDowell et al, 2008; Mort et al., 2003). The proximity to cingulate cortex, the spatial resolution of fMRI, and spatial smoothing during data preprocessing, however,

can make it difficult to determine precisely in which region activated clusters were located. Changes in context and practice, therefore, likely affect motor planning as well as conflict monitoring processes, with the adjacent regions sharing some common input/output signals.

Despite these ambiguities, both the conflict monitoring ACC and motor planning SEF showed greater BOLD signal during antisaccade trials than prosaccade trials in the current study, as mentioned above. Furthermore, this antisaccade activation in ACC decreased at the post-test MRI session. Presumably, the inherent conflict between the visually-driven response and the need to generate a volitional saccade in the opposite direction was diminished as participants became more familiar with the novel antisaccade task set and probability contexts. There was also an interaction between practice group and time point in the right ACC, with the specific practice group reducing BOLD signal over time while the general practice group showed little change. Insofar as reduced BOLD signal in this region is indicative of reduced conflict, this result implies that the specific group's extended practice with the mixed probability contexts led to more efficient task selection processes that minimized the competition between antisaccade and prosaccade task sets. With only general antisaccade practice, participants perhaps could not switch between task sets as effectively in the mixed contexts and still required cognitive control supervision to a similar degree at post-test as at baseline.

All in all, the ACC showed a moderate degree of variability in BOLD response strength across the two trial types and several contexts presented in these studies. This variability is a manifestation of the flexibility and sensitivity of cognitive control mechanisms to changing environmental conditions. When conflicting task demands and motor responses arise in an experimental paradigm, the ACC should be engaged only to the extent necessary to upregulate cognitive control processes in prefrontal and parietal cortices, which in turn modulate sensory

and motor processes in lower cortical and subcortical regions. When trial history or extended practice with a task or context leads to a strengthened task representation in these basic sensory-motor regions, less interference occurs from the opposing task set causing less conflict to be detected by the ACC.

Saccade Trial Type Probability

In Chapters 3 and 4, the context of prosaccade and antisaccade trials was manipulated by varying the probability, or relative frequency, of each trial type in a series of mixed blocks. This contextual variation was expected to bias the internal task set representations for each trial type in favor of the more probable saccade type (Massen, 2004). Previous behavioral studies in our laboratory have supported this hypothesis (Pierce et al. 2015; Pierce & McDowell, 2016), and the current studies sought to characterize the neural correlates of this trial type probability manipulation and investigate how performance changed with extended practice. Generally, low trial type probability resulted in greater BOLD signal in visual processing and control regions, and saccade practice resulted in more equivalent behavioral performance across probability blocks.

As discussed in Chapter 1, models of saccade programming describe a competition between simultaneously initiated prosaccade and antisaccade task sets that accumulate activity and race towards a motor threshold (Carpenter & Williams, 1995; Cutsuridis et al., 2007; Massen, 2004; Noorani & Carpenter, 2013). Theories disagree as to the neural implementation of this competition and the mechanism by which one task set is selected and the other inhibited. Many consider PFC to be the source of inhibition of the context-irrelevant response, although recent neurophysiological evidence suggests that PFC cytoarchitecture and structural

connections are more likely to facilitate the relevant response than to provide direct top-down inhibition (Everling & Johnston, 2013). This hypothesis implies a lateral inhibition in other regions supporting the opposing task sets, such that greater facilitation of one will lead to less activation of the other, possibly through local inhibitory interneurons. The competition may occur within parietal cortex as sensorimotor signals for opposite response directions are calculated (Anderson, Husain, & Sumner, 2008; Zhang & Barash, 2000), within FEF/SEF saccade motor neurons (Everling & Munoz, 2000), and/or within the retinotopic motor map of intermediate layers of the superior colliculus (Munoz & Everling, 2004).

Cutsuridis and colleagues (2007) favored this latter option, with minimal top-down control, because fixation neurons and location-specific activity in saccade neurons in superior colliculus can have an inhibitory influence on alternative target locations (Munoz, Dorris, Pare, & Everling, 2000; Munoz & Everling, 2004). The superior colliculus outputs to brainstem saccade-generating nuclei and since the eyes can be directed to only a single point in space at any given moment, competition between potential target locations should be resolved no later in the pathway than within this structure. Unfortunately, typical BOLD fMRI is ill-suited to capture activation in superior colliculus due to its small size and the potential for partial volume effects with neighboring cerebral spinal fluid, so the current studies could not address this issue directly. The numerous cortical outputs of the saccade network, however, certainly contribute to the resolution of this competition and the present studies focused on how the full array of sensory input, contextual information, and prior experience biased cortical activation of each saccade task set from trial to trial.

In the studies in Chapters 3 and 4, the competition between task sets was investigated by changing the relative trial type probability of prosaccade and antisaccades. This contextual

manipulation influenced the activation of each task set through the overall trial history within each block. When participants performed one trial type more frequently, its task set activation presumably was strengthened and, therefore, performed more easily when a subsequent trial also required this type of response. Thus, the usual competition between a dominant visually-driven response towards the peripheral stimulus and a novel volitionally-driven response to the mirror image location shifted according to the context in which the saccade trials were performed. During low probability trials, more antisaccade errors were generated, suggesting that the competition between opposing task sets interfered with selection of the correct trial type and resulted in the visual stimulus triggering an erroneous saccade more often. Both general cognitive control regions, such as ACC, PFC, and PPC, and task-specific visual-motor regions, such as occipital-temporal cortex and FEF/SEF, showed greater BOLD signal in blocks with low trial type probability. This effect was stronger for prosaccade trials within the three mixed contexts in Chapter 3, although antisaccades showed a similar effect when considering all four probability blocks and both time points in Chapter 4. These activation differences likely reflected greater attentional recruitment by low probability trials and the need for stronger cognitive control of task set selection. The present work thus supports the notion of a distributed competition between simple and complex saccade trial types with multiple ocular motor and cognitive control regions showing a differential response based on the trial history context defined by trial type probability.

Learning of New Task Sets and Neural Plasticity

While in Chapters 2 and 3 the effects of context on saccade behavior and brain activation were explored via paradigm design, Chapter 4 considered the context of a participant's

experience with a task set. Initially, the prosaccade task set, although unfamiliar perhaps in terms of the specific stimuli presented or eye tracking set-up, required a fundamentally instinctive response – look at a sudden onset stimulus; the antisaccade task set, in contrast, required a novel, arbitrary response – look to the mirror image location. In the third study presented here, participants completed a week of practice of the general antisaccade task alone or the specific mixed probability blocks. After this extended exposure to one or both task sets, participants responded more quickly, made fewer errors, and reduced BOLD signal across saccade circuitry for both trial types. The specific practice group also showed an activation decrease in additional regions, suggesting that they were able to further reduce the demand for attentional control of task set selection due to their greater familiarity with both task sets and the probability contexts. The general practice group exhibited little signal change in some regions, indicating that, despite behavioral improvements, perhaps they were not able to generalize practice with the antisaccade task set alone to the mixed blocks (with additional demands for maintenance of and switching between multiple task sets) as efficiently as the specific practice group. Overall, this study demonstrated the brain's ability to learn new tasks and construct internal representations that can be selected more automatically with practice and, thus, the plasticity of cognitive control systems in young adults.

During development, there are "sensitive periods" when many fundamental brain functions such as visual perception, language, or motor coordination undergo a time of rapid learning, neural growth, and reshaping of structural connections. This plasticity is critical for proper neural development, but diminishes with age to protect established skills. Children can learn to understand and speak multiple languages, for example, with relative ease, while an adult might struggle to learn a second language. Yet with sufficient practice the adult can master this

skill and many others. The brain retains some degree of neural plasticity throughout adulthood that allows an individual to continue to learn new tasks, form new memories, and change old habits. In the current work, this plasticity meant that a participant's initial performance of the antisaccade task was susceptible to improvement and that the underlying brain activation could change with learning of the task set. (Interestingly, while antisaccade performance did improve with practice in some studies (Dyckman & McDowell, 2005; Ettinger et al., 2003) including the current work, other studies indicated that antisaccade behavior may be a relatively stable individual trait (Klein & Fischer, 2005; Smyrnis, 2008).)

In Chapter 4, plasticity was observed in a cognitive control "scaffolding" network including ACC, PFC, and PPC (Chein & Schneider, 2005), which was activated at the baseline scan during antisaccade trials to support the selection of this novel task set in competition with the prosaccade task set. Yet after practice there was weak or no BOLD signal in these regions, suggesting that the task set had been learned sufficiently to allow lower visual-motor systems to execute the correct response in changing contexts with less top-down control. These findings, however, are based on the BOLD fMRI signal which does not measure neural changes directly and therefore cannot speak to particular molecular/structural modifications that may occur over time. Nonetheless, the clear reduction in signal following practice denotes a different neural-metabolic-vascular response from the baseline scan associated with increased familiarity with the saccade task sets and probability contexts. Further research with alternative neuroimaging methodologies could help clarify how activity in cognitive control regions and the saccade network changes from naïve to experienced task performance.

Open Questions

The studies presented above serve to illuminate the response properties of cognitive control of saccade tasks under varying contexts, yet some additional questions remain unresolved. One set of questions arises from the limited temporal resolution of BOLD imaging and the hemodynamic response: How do network dynamics and functional connectivity impact the observed responses? Which regions respond earliest following the presentation of the trial type cue (antisaccade vs. prosaccade)? Does this change with practice? Are there brief responses by control regions being missed entirely by the BOLD signal? Many of these possibilities could be resolved by using a technique like electroencephalography with much higher temporal resolution that captures direct electrical neural signaling (e.g., Clementz, Brahmbhatt, McDowell, Brown, & Sweeney, 2007; Clementz et al., 2010). Combining EEG with a trial type probability manipulation could provide greater insight into how context affects rapid neural signaling in cognitive control regions during saccade tasks. Even using an fMRI protocol with a shorter TR to sample the hemodynamic response with greater precision would be informative. With the current dataset, functional correlations or effective connectivity analyses across voxels could provide additional information on network organization and coherence. Alternatively, transcranial magnetic stimulation could be used to temporarily knock out individual regions to investigate how behavior and saccade network functioning change under these altered conditions (Muri, Rivaud, Vermersch, Leger, & Pierrot-Deseilligny, 1995; Nyffeler et al., 2007). If TMS was applied to the dorsolateral PFC, for example, task selection or suppression processes could be disrupted and more errors generated on low probability or task switching trials.

Other potential analyses include an examination of individual differences in response to context – do certain participants show stronger trial type probability effects or greater

improvement with practice? Do these differences correspond to overall cognitive control ability? Further studies with alternative measures of cognitive control or other cognitive processes could illuminate the specificity of these effects to saccade tasks or generalizability across tasks with similar visual, attentional, or motor demands. In theory, many of the effects reported in Chapters 2-4 should be observed in other cognitive control paradigms with general top-down processes responding to context in a similar fashion and only the sensory-motor systems differing between tasks. Many other questions could be proposed in relation to the effects of context on cognitive control of saccade tasks and ideally each new study will help build a more complete understanding of how neural systems provide such a spectrum of flexible behaviors.

Conclusions about the Role of Context in Cognitive Control

Cognitive control processes supervise execution of goal-relevant behaviors and the context of an action strongly influences the success or failure of such mechanisms. The collective history of an individual's life experiences shapes the way he/she responds to the world and recent experience in a given context affects behavior greatly. For cognitive neuroscience research, this context includes factors like paradigm design, trial order, or testing environment that may bias a participant's ability to perform the current trial effectively. In the set of studies presented in Chapters 2-4, context was manipulated by changing the task structure and task switching demands, trial type probability and task set competition, and type of task practice a participant performed. The results demonstrated that an interleaved task structure led to a strong BOLD signal in conflict-monitoring ACC during antisaccade task switch trials, while a blocked task structure led to weak ACC activation with sustained PFC activation for both trial types. Low trial type probability yielded greater BOLD signal in cognitive control and ocular-motor circuitry

putatively to support selection of the weaker task set in the competition for saccade execution. Finally, specific practice of both the simple and complex saccade trial types in the mixed probability contexts resulted in greater reduction of BOLD signal than general antisaccade-only practice, although both groups showed less activation across saccade circuitry and improved antisaccade behavior during the post-test session. In conclusion, these studies illustrate the influence of context on behavior and brain activation in simple and complex saccade tasks and highlight how the flexible nature of cognitive control adapts responses to most efficiently meet changing task demands.

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