PERFORMANCE MONITORING BY THE MEDIAL FRONTAL CORTEX

By

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Neuroscience

August, 2011

Nashville, Tennessee

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PREFACE

> I claim to be a simple individual liable to err like any other fellow mortal. I own, however, that I have humility enough to confess my errors and to retrace my steps.
>
> —Mohandas Gandhi, in Iyer and Iyer 1986

This quote exemplifies the road I have been on the past few years in pursuit of the Ph.D. Humility has kept me on this road, for there have been many errors — in and out of science — and I have had to retrace my steps numerous times when I have lost my way.

I would like to thank the following people for all that they have given during this journey: my advisor, Jeff Schall; my committee, Gordon Logan, Thomas Palmeri, and David Zald; my lab mates (past and present), Leanne Boucher, Jeremiah Cohen, Anna Garr, David Godlove, John Haitas, Richard Heitz, Melanie Lesie, Pierre Pouget, Veit Stuphorn, and Geoff Woodman; the Vanderbilt Brain Institute, the Center for Cognitive and Integrative Neuroscience, and The Meharry Vanderbilt Alliance; and my family and friends who have provided love and support while I have been engaged in this endeavor.

This work was supported by National Institutes of Health Grants F32-EY-017765, T32-MH-065782, R01-MH-55806, P30-EY-08126, and P30-HD-015052 and by Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience.

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CHAPTER I

INTRODUCTION: EXECUTIVE CONTROL AND THE FRONTAL LOBE

1.1 Introduction and background

Executive function deficits are associated with a number of psychiatric and developmental disorders (American Psychiatric Association, 1965). The hallmark of executive control — high-level, flexible, goal-directed behavior — resulting from the primate brain is one of its distinguishing characteristics. Behavioral adjustments following errors are often accompanied by the error related negativity (ERN) — a frontocentrally distributed negative going potential which peaks ∼100 ms following error responses and, thus, has been acknowledged as an index of performance monitoring. The ERN has a dipole source that is co-localized with functional activation in response to errors that is most consistently observed in the medial frontal cortex (reviewed by Hester et al. 2004; Taylor et al. 2007). Converging evidence from lesion, monkey neurophysiology, human neurophysiology, and functional imaging investigations has focused conversations regarding performance monitoring on the medial frontal lobe. The same evidence has resulted in diverging hypotheses regarding the functional significance of the medial frontal lobe and the neural signals observed there. The work described in this thesis describes behavioral evidence of performance monitoring in macaque monkeys and tests the specific predictions resulting from hypotheses of the functional significance of the ERN and other neural signals observed in the medial frontal cortex using electrical field potentials acquired from macaque

monkeys performing a saccade stop-signal task.

1.1.1 Chapter overview

Numerous experiments have sought to test existing hypotheses of the functional significance of the neural signals observed in the medial frontal cortex (reviewed by Botvinick et al. 2004; Ridderinkhof et al. 2004; van Veen and Carter 2006). This extensive literature can be summarized with the statement that each hypothesis remains plausible, and none can be excluded entirely. One reason for this lack of conceptual resolution is the low spatial or temporal resolution of event related potentials (ERP) and functional magnetic resonance imaging (fMRI) measures. The opportunity to carry out invasive studies in non-human primates can contribute to resolving among these alternative hypotheses. In fact, single-unit activity interpreted as performance monitoring signals have been observed in the supplementary eye field (SEF) and anterior cingulate cortex (ACC) in macaque monkeys performing a variety of behavioral tasks (Amiez et al., 2006; Isomura et al., 2003; Ito et al., 2003; Stuphorn et al., 2000; Koyama et al., 2000, 2001; Nakamura et al., 2005; Niki and Watanabe, 1979; Procyk and Joseph, 2001; Procyk et al., 2000; Shidara and Richmond, 2002, 2005). However, scalp potentials are the summation of intracranial local field potentials and not unit discharges (reviewed by Nunez and Srinivasan 2005). Therefore drawing conclusions based on converging evidence from single unit studies in non-human primates and ERP or fMRI studies in humans entails several uncertain inferences.

The goal of this thesis was to establish a link between monkey single-unit data and human ERP and fMRI data by characterizing the behavioral adjustments of humans

and monkeys performing the stop signal task and to determine whether electrical field potentials signaling performance monitoring are observed in the medial frontal cortex of macaque monkeys performing the saccade stop signal task. This chapter will first describe the hypotheses of the functional significance of the ERN and other the neural signals observed in the primate medial frontal cortex, the stop-signal paradigm and how it has been used to examine performance monitoring, and ,finally, the physiology of functional areas of the frontal lobe that have been probed using the stop signal task.

1.2 The ERN and hypotheses of its functional significance

The neural signals that monitor and allow for adjustments in behavior have been the subject of much interest in the past 40 years. Rabbitt (1966b) provided the first experimental evidence of such flexible, goal-directed behavior and suggested the importance of a system that detected errors and adjusted performance. Error trials in speeded response tasks, which were often accompanied by emotional reactions of frustration, resulted in slower responses in the following trials (Rabbitt, 1966b,a; Rabbitt and Phillips, 1967; Laming, 1979). Since the seminal work of Rabbitt (1966b), a number of human behavioral studies examined the relationship between errors and response times (e.g., Hale 1967; Rabbitt 1968a,b; Remington 1969). The robust nature of post-error slowing has led to its wide acceptance as a result of cognitive control, and is used as a marker for cognitive control in clinical studies (e.g., Bogte et al. 2007; Kerns et al. 2005; Sergeant and van der Meere 1988; Schachar et al. 2004; but see Mathalon et al. 2002).

Compelling evidence for the role of the ERN in performance monitoring has been the relationship between ERN amplitude and task demands. The ERN is evoked during a variety of speeded, cognitively demanding tasks (e.g.,Go/No-Go tasks, Stroop task, Eriksen flanker task, error awareness task, stop-signal task, and the antisaccade task; reviewed by Taylor et al. 2007). Gehring et al. (1993), in his initial report of the potential, observed that the ERN amplitude is correlated with the importance that subjects place on minimizing errors. For example, when subjects are instructed to emphasize accuracy over speed, the magnitude of the ERN increases (Falkenstein et al., 2000; Gehring et al., 1993). The ERN is generally followed by a P300-like positive going potential, the error positivity (Pe), which is a slow positive deflection in the EEG that reaches its maximum between 200 and 400 ms after the error response (e.g., Falkenstein et al. 2000; Nieuwenhuis et al. 2001). Although both the ERN and the Pe are related to error responses, the Pe is generally considered to be independent of the ERN (Falkenstein et al., 2000) and may be related to the affective evaluation of the error (e.g., Nieuwenhuis et al. 2005). Like post-error slowing, the robust nature of the ERN has led to its wide acceptance as an index of cognitive control, and is used as a marker for cognitive control in clinical studies (e.g., Bogte et al. 2007; Kerns et al. 2005; Sergeant and van der Meere 1988; Schachar et al. 2004; but see Mathalon et al. 2002).

Since the ERN was first reported, other similar electrophysiological components with similar localization and apparent evaluative function have been identified. The medial frontal feedback negativity (fERN), which occurs approximately 250 ms after the subject receives feedback has provided additional evidence for an evaluative role

of this signal in monitoring performance (e.g., Badgaiyan and Posner 1998; Gehring and Willoughby 2002a; Holroyd et al. 2002; Mars et al. 2004; Miltner et al. 1997). Consistent with the fact that the ERN amplitude is correlated with the importance that subjects place on minimizing errors, studies of the fERN have provided evidence that this ERP component is sensitive to the relative value of the outcome of task performance (Gehring and Willoughby, 2002a; Hajcak and Nieuwenhuis, 2006; Holroyd et al., 2004; Nieuwenhuis et al., 2004; Oliveira et al., 2007). The N200 or N2 potential is also modulated by task demands and has also been suggested as an index of performance monitoring (e.g., van Boxtel et al. 2001; Yeung et al. 2004).

A number of hypotheses have been proposed to explain the functional significance of the ERN and other neural signals observed in the primate medial frontal cortex. The initial account of the functional significance of the error-monitoring hypothesis proposes that the ERN reflects a comparison between the representations of the overt error response and the correct response (Falkenstein et al., 1991; Gehring et al., 1993). Two other hypotheses are based on computational models which are grounded in anatomical and physiological data. The conflict theory posits the medial frontal potential represents a specific occurrence of response conflict monitoring (Botvinick et al., 2001; Carter et al., 1998). The reinforcement learning theory (Holroyd et al., 2002) hypothesizes that the ERN is an evaluative function signifying worse than expected events.

1.2.1 *The Error Monitoring Hypothesis of the ERN*

The error-monitoring hypothesis proposes that the ERN reflects a comparison between the representations of the overt error response and the correct response (Falkenstein et al., 1991; Gehring et al., 1993), a function comparable to other midline negativities signaling mismatch (Näätänen et al., 1978) and the N400 (Kutas and Hillyard, 1984). Two separate but similar models of error-related processing have been proposed to explain the specifics of the ERN process (Falkenstein et al., 1991; Bernstein et al., 1995). In both models, the two main components at the heart of the error-processing system are a monitoring system that detects errors and a remedial action system. The comparator compares the representations of the correct or appropriate response with that of the actual response. For any hypothesis of cognitive control to be complete, it has to provide an account of how the system determines when control is required. It is important to note that these two models are not computational models, therefore the interpretation of neural signals and the underlying processes is speculative and cannot demonstrate the sufficiency of the hypothesis to account for them.

1.2.2 *The Response Conflict Monitoring Hypothesis*

The conflict-monitoring hypothesis proposes that control is recruited based on the occurrence of conflicts in information processing; specifically, the coactivation of mutually incompatible response processes (Botvinick et al., 2001, 2004). This hypothesis was formulated originally based on fMRI evidence for a conflict-monitoring function

of the ACC (Botvinick et al., 1999; Carter et al., 1998, 1999). ACC activation is observed in tasks calling for the overriding of prepotent but task-irrelevant responses, tasks requiring the participant to choose among a set of equally permissible responses, and tasks that lead to the commission of errors (reviewed by Botvinick et al. 2001, 2004; Yeung et al. 2004; Carter and van Veen 2007). Specifically, (Botvinick et al., 2001) proposed the existence of a system which monitors for the occurrence of conflicts in information processing, a function referred to as conflict monitoring. The conflict monitoring system first evaluates current levels of conflict. This information triggers centers responsible for control, for example the lateral prefrontal cortex, resulting in an adjustment of the strength of their influence on processing.

Botvinick et al. (2001) defined response conflict as the coactivation of incompatible responses. The Hopfield energy from computer simulations using previously and independently implemented computational models of single tasks in which ACC activation had been reported as the measure of conflict. The Hopfield energy is simply the energy in a recurrent neural network resulting from the coactivation mutually inhibiting units. This measure of conflict is minimal when only one of the units is active and maximal when both units are equally active. The resulting simulated modulation of the response conflict was consistent with the pattern of ACC activation observed in the same context. Furthermore, when conflict was used as the feedback signal in these models, the resulting simulated behavior closely resembled trial history effects previously reported in a variety of tasks.

1.2.3 *The Reinforcement Learning Hypothesis of the ERN*

The reinforcement learning (RL) hypothesis of the ERN proposes that this frontocentral negativity, which is also elicited by feedback indicating error, loss, or punishment (Gehring and Willoughby, 2002a; Miltner et al., 1997) and the unexpected absence of reward (Holroyd and Yeung, 2003), is generated by the ACC. This theory was inspired in part by Schultz (2002) who observed dopamine neurons that were modulated by stimuli that predict a reward and reduce activity when an expected reward does not occur (see also Zaghloul et al. 2009). This result was interpreted in relation to formal issues of animal learning theory, which describe the acquisition of associations between arbitrary stimuli and primary motivating events (reinforcers) in classical conditioning paradigms (Rescorla and Wagner, 1972; Dickinson, 1981). According to this rule, stimuli gain associative strength over consecutive trials by repeated pairings with a primary motivating event. This potential use of prediction error signals has been explored in temporal difference reinforcement models which implement the Rescorla-Wagner rule (Sutton and Barto, 1981). The temporal difference teaching signal is similar to the dopamine reward signal and networks using an explicit temporal difference teaching signal similar to dopamine neurons learn complex behavioral tasks, such as foraging behavior (Montague et al., 1995), decision making (Montague et al., 1996), sequential movements (Suri and Schultz, 1998), and delayed responding (Suri and Schultz, 1999). Holroyd et al. (2002) proposed that both the response ERN and the feedback ERN are produced by a dopamine system for RL. The reduction in dopaminergic activity in the absence of an expected reward

disinhibits activity in the medial frontal cortex, specifically in the ACC, because the negative scalp potential generator is localized in or near the ACC (Miltner et al. 1997; van Veen and Carter 2002; see also Brown and Braver 2005).

1.3 The Stop Signal Paradigm, the Race Model, and Performance Monitoring

The stop signal or countermanding paradigm, which includes both a task design and a theoretical construct, was developed to investigate the control of action (reviewed by Logan 1994; Figure 1.1). Although many variations in the stimuli and effectors have been used in the stop signal task, the requirements of the task are quite simple. The stop-signal task probes the ability to control action by requiring subjects to withhold a planned movement in response to an infrequent stop signal which they do with variable success depending on the delay of the stop signal.

The saccade stop signal task used in the work described in this thesis is illustrated in Figure 1.1. All trials began when the monkey fixated a centrally located target for a variable interval. Simultaneously, the fixation stimulus was extinguished and a peripheral target was presented at one of two diametrically opposed locations in opposite hemifields, cuing the monkey to make a single saccade to the target. In no stop signal trials, the monkey was reinforced for making a saccade as quickly as possible to the target and fixating it. On stop signal trials, the central fixation target reappeared after a delay, referred to as the stop signal delay, instructing the monkey to inhibit saccade initiation. This happened on a minority trials. Two outcomes are possible on stop signal trials; the monkey could either make a saccade (known as a noncancelled, or signal-respond, trial) or not (known as cancelled, or signal-inhibit,

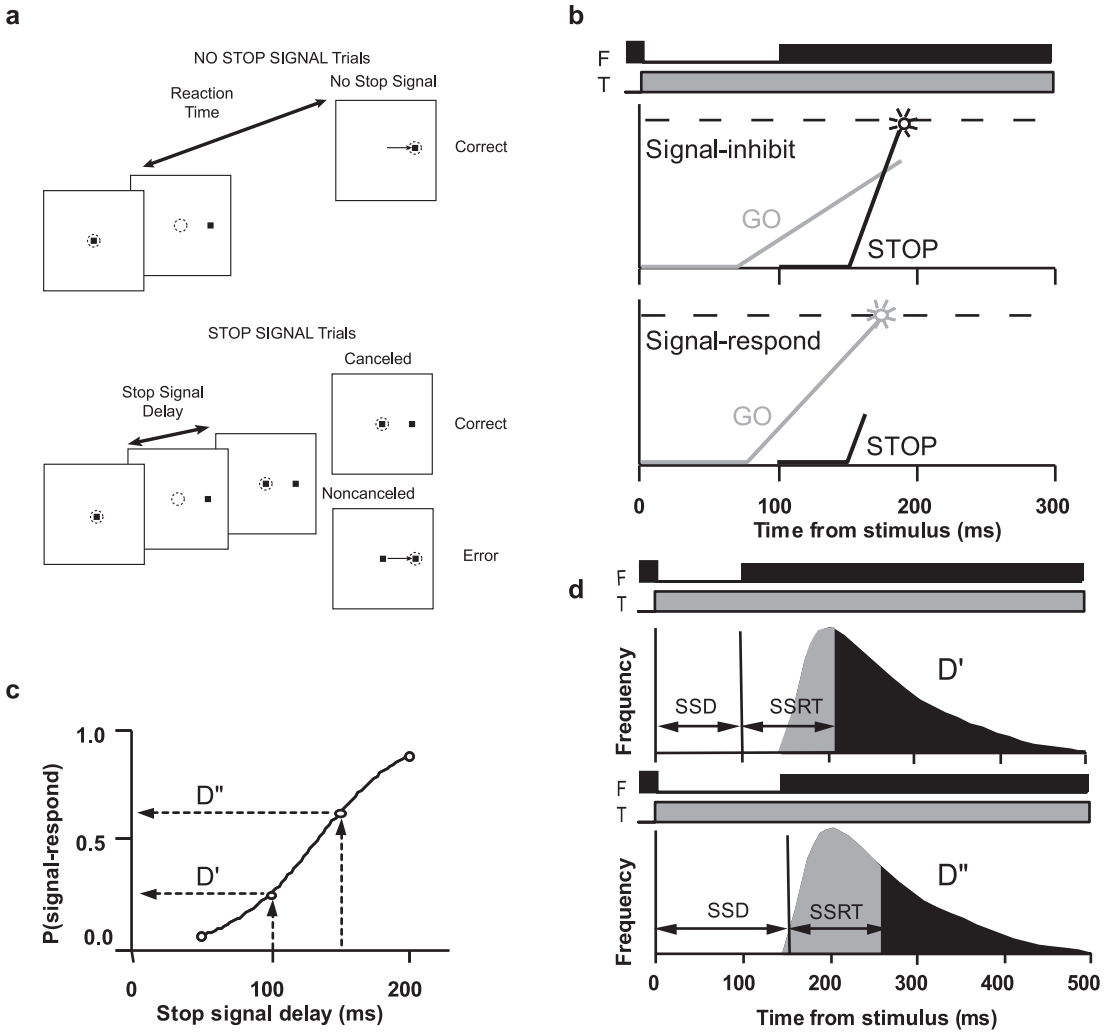

Figure 1.1: a: Trial displays for saccade countermanding task. Dotted circle indicates focus of gaze at each interval; arrow, the saccade. All trials began with presentation of a central fixation spot. After fixation of this spot for a variable interval, it disappeared simultaneous with presentation of a target on the left or right. In no stop signal trials, a single saccade to the peripheral target was reinforced as the correct response. In stop signal trials, the fixation spot reappeared after a variable stop signal delay. Maintained fixation was reinforced as the correct response; these are referred to as cancelled (or signal-inhibit) trials. If a saccade was produced in spite of the stop signal, no reinforcement was given; these errors are referred to as noncancelled (or signal-respond) trials.b. Race model outcome when $rt_{go} > rt_{stop}$ + SSD, resulting in a signal-inhibit trial (top panel), and when $rt_{go} < rt_{stop}$ + SSD, resulting in a signal-respond trial (bottom panel). Above each graph is a timeline marking the onset and offset of the fixation (F) and target (T). c: An idealized inhibition function plotting the proportion of signal-respond trials as a function of SSD. D' and D" indicate the proportion of signal-respond trials at SSDs of 100 ms and 150 ms, respectively. d: Schematic illustrating how stop-signal reaction time (SSRT) is calculated at two different SSDs by the integration method. With permission from Boucher et al. (2007a).

trials). Monkeys were reinforced for maintaining fixation on the stop signal. A saccade to the target on a stop signal trial was incorrect, not reinforced, and resulted in a timeout.

Based on a race between a GO and a STOP process with independent stochastic finish times, (Logan et al., 1984) demonstrated that the time needed to cancel a movement, the stop signal reaction time (SSRT), can be estimated from the distribution of response times when no stop signal is presented and the probability of responding given that a stop signal occurred, the inhibition function. SSRT can be estimated using various methods (reviewed by Band et al. 2003a; Logan 1994). This race model has been implemented in a linear rise to threshold model framework (Hanes and Carpenter, 1999) and in a network of interacting units with delayed potent inhibition (Boucher et al., 2007b).

The application of the race model to stop signal data provides an advantage over other paradigms requiring inhibition because it allows investigators to estimate the time required to inhibit, SSRT. De Jong et al. (1990) were the first to use the stop signal task to examine the ERP correlate of movement preparation, the lateralized readiness potential (LRP; Kornhuber and Deecke 1965; Vaughan Jr et al. 1968; Kutas and Donchin 1974). Later, Naito and Matsumura (1994a, 1996) examined potentials evoked by the stop signal in the context of selective stopping. Most investigations employing the stop signal task have required subjects to respond manually (van den Wildenberg et al., 2003; Kok et al., 2004; Penney, 2004; Albrecht et al., 2005; Bekker et al., 2005a,c; Kenemans et al., 2005; Liotti et al., 2005; Dimoska et al., 2006; Ramautar et al., 2006a; Schmajuk et al., 2006; Dimoska and Johnstone, 2007; Johnstone

et al., 2007a,b; Pliszka et al., 2007; Dimoska and Johnstone, 2008). It is commonly observed across experimental conditions and response modalities that subjects‘ response times tend to increase in the context of the countermanding task relative to that in simple response time tasks (e.g., Logan 1981; Logan and Burkell 1986; Mirabella et al. 2006; van den Wildenberg et al. 2003; but see Özyurt et al. 2003). ERPs have also been examined in the context of the stop signal task (van den Wildenberg et al., 2003; Kok et al., 2004; Penney, 2004; Albrecht et al., 2005; Bekker et al., 2005a,c; Kenemans et al., 2005; Liotti et al., 2005; Dimoska et al., 2006; Ramautar et al., 2006a; Schmajuk et al., 2006; Dimoska and Johnstone, 2007; Johnstone et al., 2007a,b; Pliszka et al., 2007; Dimoska and Johnstone, 2008). Thus far, the only investigation to examine single unit activity during a manual stop signal task has been Scangos and Stuphorn (2010). In addition to examining movement preparation and inhibition, the stop signal task has been used to examine inhibitory control in other contexts, such as inhibition of return (Taylor and Ivanoff, 2003), Stroop and Eriksen flanker tasks (Verbruggen et al., 2004), and task switching (Verbruggen et al., 2005). The stop signal task has also been used to examine patients with ADHD (Tannock et al., 1989; Quay, 1997; Brandeis et al., 1998; Overtoom et al., 2002; Konrad et al., 2004; Bekker et al., 2005c; Kenemans et al., 2005; Liotti et al., 2005; Johnstone et al., 2007a; Pliszka et al., 2007) and, recently, has been selected for translation for use in clinical trials Barch et al. (2009). Like the ERN and post-error slowing, the robust nature of stop signal task performance has led to its wide acceptance as a marker for cognitive control in clinical studies (e.g., Bogte et al. 2007; Kerns et al. 2005; Sergeant and van der Meere 1988; Schachar et al. 2004; but see Mathalon et al. 2002).

1.3.1 Performance monitoring and post error slowing

Post-error slowing in choice tasks has been regarded as evidence of executive control (e.g., Laming 1979; Rabbitt 1966a; Rabbitt and Phillips 1967; Braver et al. 2007). The robust nature of post-error slowing is now widely accepted as a cognitive control effect, and is used as a marker for cognitive control in clinical studies (e.g., Bogte et al. 2007; Kerns et al. 2005; Sergeant and van der Meere 1988). Post error slowing and other sequential dependencies have been observed in macaque monkeys performing a variety of tasks (Dorris et al. 1999, 2000; Procyk et al. 2000; see also Bichot and Schall 1999; reviewed by Fecteau and Munoz 2003). However, although post error slowing occasionally coincides with improved accuracy following errors (Rabbitt, 1966b; Laming, 1968; Marco-Pallars et al., 2008), King et al. (2010) found no such relationship and several studies have even reported decreased post-error accuracy (Rabbitt, 1977; Laming, 1979; Hajcak and Simons, 2008). Note that alternative accounts of the mechanism underlying post error slowing and sequential dependencies exist. For example, it has been suggested that post error slowing may reflect persistence of a breakdown in processing that contributed to the error (Gehring and Fencsik, 2001) or error evoked arousal that interferes with task preparation (Carp et al., 2009). Recent evidence suggests that it may merely reflect an unspecific orienting response (Notebaert et al., 2009; Castellar et al., 2010).

When subjects perform the stop signal task sequential dependencies have also been observed. Subjects overall response times are slower when stop signal trials are presented compared when just the no stop signal trials (primary task) are presented.

Specifically, the overall delay of response times following stop signal trials has been reported for saccades (Cabel et al., 2000; Kornylo et al., 2003) and manual responses (Rieger and Gauggel, 1999; Schachar et al., 2004). In fact, delayed manual response times following noncancelled and cancelled stop signal trials have been reported in choice tasks (Rieger and Gauggel, 1999; Schachar et al., 2004) and reaching movements (Mirabella et al., 2006). Most recently, Nelson et al. (2010) described how nonindependence and nonstationarity of reaction times might impact the measures of trial-to-trial adaptations of response times described in Chapter II.

1.4 The Stop Signal Paradigm and the Frontal Cortex

Previous work has implicated a number of structures in the frontal lobe as to playing a role in the control saccadic eye movements (Figure 1.2). Saccades can be elicited by low-intensity microsimulation of the frontal eye field (FEF; e.g., Bruce et al. 1985) and the supplementary eye field (SEF; e.g., Schlag and Schlag-Rey 1987). Based on its dense reciprocal connections with the SEF and weak connections with the FEF (Huerta and Kaas, 1990), a subdivision of the anterior cingulate cortex (Area 24c of Matelli et al. 1991) has likewise been implicated as playing a role in the control of saccadic movements. The physiology of each of these areas have been examined in monkeys performing the saccade stop signal task.

1.4.1 Frontal Eye Field

The frontal eye field (FEF), located in the rostral bank of the arcuate sulcus in macaque monkeys, participates in the transformation of visual signals into sac-

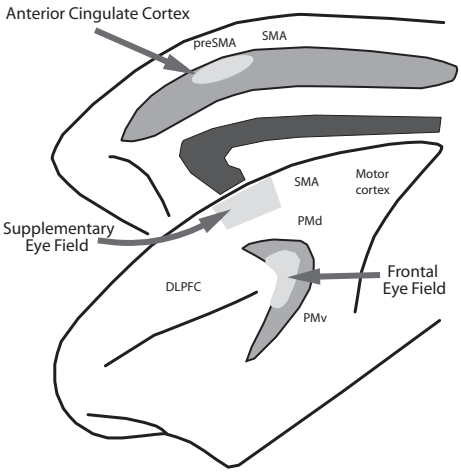

Figure 1.2: Dorsolateral (lower) and mesial (upper) views of the macaque frontal cortex showing the location of the frontal eye field, the supplementary eye field, and the region of anterior cingulate cortex described in this review. For reference, the general location is shown of the primary motor cortex, supplementary motor area (SMA), presupplementary motor area (preSMA), dorsal premotor cortex (PMd), ventral premotor cortex (PMv), and dorsolateral prefrontal cortex (DLPFC). Light gray highlights opened sulci. With permission from Schall and Boucher (2007).

cade motor commands (reviewed by Schall,1997). Single unit recordings in the FEF of monkeys trained to make saccades to visual targets have revealed neurons that have visual responses which participate in the selection of visual targets for saccades (reviewed by Schall and Thompson 1999). Two other functional subpopulations of neurons have been observed in the FEF during gaze shifts. Movement neurons in the FEF exhibit increased discharge before and during saccades (Bruce and Goldberg, 1985; Hanes and Schall, 1996; Schall, 1991a) while fixation neurons are active during fixation and exhibit decreased discharge preceding saccades (Sommer and Wurtz, 2000; Hanes et al., 1998). FEF neurons innervate the superior colliculus (Segraves and Goldberg, 1987; Sommer and Wurtz, 2000) and the neural circuit in the brainstem that generates saccades (Segraves, 1992).

Hanes et al. (1998), the first study to apply the race model to single unit activity during the saccade stop signal task, examined the sufficiency of FEF neurons to control the initiation of saccadic eye movements. Applying the race model to neuronal activity acquired in the context of the stop signal task, provided clear evidence that movement and fixation neurons in FEF generate signals sufficient to control the production of gaze shifts. Saccades were initiated if and only if the activity of FEF movement neurons reach a specific and constant threshold activation level which is independent to the response time (Hanes and Schall, 1996; Brown et al., 2008). Movement neurons whose activity increased as saccades were prepared, decayed in response to the stop signal before the SSRT elapsed. Fixation cells that decreased firing before saccades exhibited elevated activity in response to the stop signal before the SSRT elapsed. The majority of visual neurons, on the other hand, did not discharge differently when saccades were initiated versus inhibited. The visual neurons that did discharge differentially when saccades were initiated versus inhibited, did so well after the SSRT had elapsed. Paré and Hanes (2003) observed parallel results for visual, movement, and fixation neurons in the superior colliculus.

Performance in countermanding tasks can be accounted for by a race between GO and STOP processes (Logan et al., 1984); in the saccade stop signal task this race is accomplished through the interaction between gaze-shifting and -holding circuits in the FEF and SC (Hanes et al., 1998; Paré and Hanes, 2003). In fact, an interactive race model with mutual inhibition between a GO unit and a STOP unit fits performance data as well as the independent race if and only if the timing of modulation of the GO and STOP units correspond to the actual modulation times of movement

and fixation neurons (Boucher et al., 2007b). In this framework, the coactivation of movement GO and fixation (STOP) units engenders response conflict. Now, cancelled trials include a period during which movement (GO) and fixation (STOP) neurons are coactive; this period of coactivation does not occur in noncancelled error trials because the fixation neurons (and the STOP unit in the model) do not turn on before the movement neurons (and the GO unit in the model) reach the threshold of activation to trigger the movement. Furthermore, the magnitude of coactivation of movement GO and fixation (STOP) units in cancelled trials increases as the probability of a noncancelled saccade increases; this occurs because the activation of the movement GO units grow progressively closer to the threshold. Thus a given amount of activation of fixation (STOP) units sufficient to inhibit the growing activation of movement GO units multiplied by the magnitude of activation of movement GO units will result in higher response conflict.

1.4.2 Supplementary Eye Field

The SEF is an area on the dorsomedial convexivity of the frontal cortex that seems to parallel the FEF in many ways. Like the FEF, the SEF provides input to ocular motor structures in the striatum, superior colliculus, and brainstem (Huerta and Kaas, 1990). The activity of neurons in the SEF are modulated by visual or auditory stimuli, while other SEF neurons are modulated preceding and during saccades (e.g., Schall 1991b; Schlag and Schlag-Rey 1987). Other studies have reported more complex functional properties of SEF neurons (e.g., Chen and Wise 1995b,a; Olson and Gettner 1995; Schlag-Rey et al. 1997; Mushiake et al. 1996; Lu et al. 2002).

Stuphorn et al. (2000, 2010) examined single unit activity during the saccade stop signal task to determine the sufficiency of SEF neurons to control the initiation of saccadic eye movements. Like the FEF movement neurons, the activity of SEF movement neurons increased as saccades were prepared; However, unlike their counterparts in the FEF, these neurons do not exhibit a reliable threshold and vanishingly few neurons in the SEF generate signals that are sufficient to control gaze (Stuphorn et al., 2010).

The countermanding task provides a novel dissociation of behavior from reinforcement that provides leverage when testing the functional significance of neural signals. On trials with no stop signal, monkeys received positive reinforcement following a saccade to the target. On trials with a stop signal, monkeys earned reinforcement when the saccade to the target for maintaining fixation on cancelled trials. Identical actions (saccades to the target) can yield different outcomes (correct reinforced no stop signal saccades or error noncancelled saccades without reinforcement). Recall that the ERN is a response locked ERP which is more negative for error versus correct responses. We have, on a small random fraction of trials, withheld earned reinforcement (no stop signal and cancelled trials without reinforcement), delivered unexpected reinforcement (noncancelled saccades that resulted in reinforcement in the inter-trial interval), and delivered unexpected additional reinforcement (reinforced no stop saccades and cancelled trials that resulted in reinforcement in the inter-trial interval). Recall that the feedback related ERN is a stimulus locked ERP which is more negative for negative versus positive feedback. These conditions permit the distinction between neuronal signals related to producing the behavioral response and those

related to the reinforcement of that response.

Although SEF movement neurons do not provide signals sufficient to control gaze, separate subpopulations of single units were identified which signaled saccade errors and reinforcement (Stuphorn et al., 2000). Recall that response conflict occurs when movement and fixation neurons are coactive. Furthermore, the magnitude of this coactivation, response conflict, increases with the probability of noncancelled saccades. Stuphorn et al. (2000) identified another subpopulation of neurons that exhibited an elevated discharge rate specifically during cancelled stop signal trials after SSRT had elapsed. The magnitude of this discharge rate was correlated with the probability of noncancelled saccades. This pattern of activity was interpreted as conflict related activity.

1.4.3 Anterior Cingulate Cortex

The ACC is a heterogeneous structure that extends from primary motor cortex to and around the rostrum of the corpus callosum (e.g., Palomero-Gallagher et al. 2008; Vogt et al. 2005). The region of the ACC in which the data discussed in this thesis is a subdivision of the anterior cingulate cortex (Area 24c of Matelli et al. 1991). Signals in the ACC can influence the ocular motor system because the rostral cingulate cortex of monkeys is oligosynaptically connected to extraocular motoneurons (Moschovakis et al., 2004). The ACC is only weakly connected with the FEF (Barbas1981b; Huerta1990,Stanton1993,VanHoesen1993,Vogt1987,Vogt1987a) and does not project to the SC (Fries, 1984). Other routes for the ACC to influence saccade production are available. First, the region of the ACC is reciprocally connected with the SEF

(e.g., Huerta and Kaas 1990; Luppino et al. 2003). Second, the ACC might also influence performance through connections with prefrontal areas 9 and 46 (Barbas and Pandya, 1989; Selemon and Goldman-Rakic, 1988; Vogt et al., 1987), but the role of these areas in saccade countermanding has not been investigated so no more can be inferred at this time.

Ito et al. (2003) examined ACC single unit activity during the saccade stop signal task. Visual neurons were observed in ACC while movement neurons were not (Pouget et al., 2005). Like the SEF, single-unit activity signaling errors and reinforcement was observed in the ACC, but, unlike SEF, no neurons signaled response conflict (Ito et al., 2003).

1.5 Overview of chapters

This chapter has presented an overview of the background and rationale for the body of work contained in this thesis. Although post error slowing is considered a robust effect, response time adjustments and improved accuracy following errors are not always observed in speeded response time tasks. The hypotheses of the functional significance of the ERN, particularly those that are based on computational models, provide a framework of hypotheses that can be used to test neural signals. The stop signal task has been used in a variety of species and numerous effectors to examine the control of movement and the outcome has been a consistent pattern of results that can be explained by a simple race model. Of the brain structures probed with the countermanding paradigm, only the physiology of movement and fixation cells in the FEF and SC fit the criteria for signals sufficient to control gaze shifts. Boucher

et al. (2007a) has provided a simple, competitive network that accounts for behavior independent race model and the neurophysiology of movement and fixation neurons in the FEF and SC. Based on Botvinick et al. (2001) definition of response conflict, the coactivation of interacting GO and STOP units is the measure of response conflict in the stop signal task. Hence, the neural signals acquired while monkeys perform the stop signal task can be examined using this framework.

Chapter II presents behavioral evidence of executive control in the form of response time adjustments and the probability of responding from humans and macaque monkeys in a saccade countermanding task that was influenced by stimulus and performance history. Chapters III and IV describe intracranial local field potentials recorded in the ACC and SEF of macaque monkeys performing a saccade countermanding task. The results provide clear evidence that error-, feedback-, and conflict-related signals are carried by the local field potentials in the macaque medial frontal cortex. Chapter V describes an extracranial error-related ERP component similar to that found in humans in macaque monkeys performing a saccade countermanding task. Altogether, the studies contained in this thesis (1) describe behavioral evidence of executive control in monkeys and humans in the context of the saccade stop signal task, (2) electrophysiological evidence of homologues of the ERN in the LFPs and ERPs of monkeys that potentially monitor performance.

CHAPTER II

INFLUENCE OF HISTORY ON SACCADE COUNTERMANDING PERFORMANCE

2.1 Abstract

The stop-signal or countermanding task probes the ability to control action by requiring subjects to withhold a planned movement in response to an infrequent stop signal which they do with variable success depending on the delay of the stop signal. We investigated whether performance of humans and macaque monkeys in a saccade countermanding task was influenced by stimulus and performance history. In spite of idiosyncrasies across subjects several trends were evident in both humans and monkeys. Response time decreased after successive trials with no stop signal. Response time increased after successive trials with a stop signal. However, post-error slowing was not observed. Increased response time was observed mainly or only after cancelled (signal inhibit) trials and not after noncancelled (signal respond) trials. These global trends were based on rapid adjustments of response time in response to momentary fluctuations in the fraction of stop signal trials. The effects of trial sequence on the probability of responding were weaker and more idiosyncratic across subjects when stop signal fraction was fixed. However, both response time and probability of responding were influenced strongly by variations in the fraction of stop signal trials. These results indicate that the race model of countermanding performance requires extension to account for these sequential dependencies and provide a basis

for physiological studies of executive control of countermanding saccade performance.

[1]

2.2 Introduction

The stop signal or countermanding paradigm, which includes both a task design and a theoretical construct, was developed to investigate the control of action (see Logan 1994). In addition to examining movement preparation and inhibition, the stop signal task has been used to examine inhibitory control in other contexts, such as inhibition of return (Taylor and Ivanoff, 2003), Stroop and Eriksen flanker tasks (Verbruggen et al., 2004), and task switching (Verbruggen et al., 2005). Many investigators have used an oculomotor version of the countermanding task that requires a subject to cancel a planned saccade at various degrees of preparation when presented with an imperative stop signal (Armstrong and Munoz, 2003; Asrress and Carpenter, 2001; Cabel et al., 2000; Curtis et al., 2005; Hanes and Carpenter, 1999; Hanes et al., 1998; Hanes and Schall, 1995; Kornylo et al., 2003; Logan and Schulkind, 2000; Paré and Hanes, 2003; Stuphorn et al., 2000). It is commonly observed across experimental conditions and response modalities that subjects‘ response times tend to increase in the context of the countermanding task relative to that in simple response time tasks (e.g., Logan 1981; Logan and Burkell 1986; Mirabella et al. 2006; van den Wildenberg et al. 2003; but see Özyurt et al. 2003.

[1]This chapter was published as Emeric EE, Brown JW, Boucher L, Carpenter RHS, Hanes DP, Harris R, Logan GD, Mashru RN, Pare M, Pouget P, Stuphorn V, Taylor TL, Schall JD. Influence of history on saccade countermanding performance in humans and macaque monkeys. *Vision Res* 47: 35-49,2007.

Based on a race between a GO and a STOP process with independent stochastic finish times, Logan and Cowan (1984) demonstrated that the time needed to cancel a movement, the stop signal reaction time (SSRT), can be estimated from the distribution of response times when no stop signal is presented and the probability of responding given that a stop signal occurred. This race model has been implemented in a linear rise to threshold model framework (Hanes and Carpenter, 1999) and in a network of interacting units with delayed potent inhibition (Boucher et al., 2007b).

The race model of countermanding performance makes no assumptions regarding the effect of stimulus and performance history on the outcome of subsequent trials. However, a number of studies have shown that the probability of responding and response times vary according to recent trial history in speeded response tasks requiring saccades (Carpenter, 2001; Dorris et al., 2000, 1999; Jüttner and Wolf, 1992; Kornylo et al., 2003; Paré and Munoz, 1996). Furthermore, post-error slowing in choice tasks has been regarded as evidence of executive control (e.g., Laming 1979; Rabbitt 1966a; Rabbitt and Phillips 1967). In addition to these trial-to-trial variations in response time, human subjects increase response times with increases in the global fraction of stop signal trials, and these changes in response times are accompanied by changes in the probability of responding (Logan, 1981; Logan and Burkell, 1986; Ramautar et al., 2004). Some performance adjustments according to trial history in the stop signal task have been reported for saccades (Cabel et al., 2000; Curtis et al., 2005; Kornylo et al., 2003; Özyurt et al., 2003) and for manual responses (Li et al., 2005; Rieger and Gauggel, 1999; Schachar et al., 2004), but a systematic analysis of sequential effects during saccade countermanding has not been performed.

The purpose of the present study was to determine if and characterize how adjustments in response times in the countermanding task are affected by stimulus (stop signal versus no signal) and performance history (correct versus errant saccades) and if these adjustments lead to a decreased probability of responding on stop signal trials. The results indicate that shifts in the probability of responding are the result of shifts in response time, which are influenced by both recent and long-term trial history. Some of these results have been presented in abstract form.

2.3 Methods

2.3.1 Macaque data collection

Data were collected from four male rhesus monkeys (*Macaca mulatta*; 7−12 kg) and two male bonnet monkeys (Macaca radiata: 8−10 kg) in two laboratories that were cared for in accordance with USDA and Public Health Service Policy on the humane care and use of laboratory animals. All surgical procedures and electrophysiological techniques have been described previously (Hanes et al., 1998; Paré and Hanes, 2003).

The experiments were under computer control to present stimuli, record eye movements, and deliver reinforcement. Detailed descriptions of the behavioral training and tasks and the methods used to collect these data have been described in detail (Hanes et al., 1998, 1995; Paré and Hanes, 2003). Eye position was monitored while monkeys were head-restrained and seated in an enclosed chair within a magnetic field via a scleral search coil. The fixation spot subtended 0.25-0.30° of visual angle, and the

target stimuli subtended between 0.25 and 3.00° of visual angle, depending on their eccentricity and had a luminance of 2, 10, or 30 cd/m^2 on a < 0.1 or 1 cd/m^2 background. Each animal was tested for approximately 4 h a day, 5 days a week. During testing, water or fruit juice was given as positive reinforcement. Access to water in the home cage was controlled and monitored. Fluids were supplemented as needed.

The countermanding task is illustrated in Fig. 2.1. All trials began when the monkey fixated a centrally located target for a variable interval (500−800 ms). Simultaneously, the fixation stimulus was extinguished and a peripheral target was presented at one of two diametrically opposed locations in opposite hemifields, cuing the monkey to make a single saccade to the target. In no stop signal trials, the monkey was reinforced for making a saccade within 500−700 ms to the target and fixating the target for 200−400 ms. On stop signal trials, the central fixation target reappeared after a delay, referred to as the stop signal delay, instructing the monkey to inhibit saccade initiation. This happened on 10-70% of the trials, depending on the block condition. Two outcomes were possible on stop signal trials; the monkey could either make a saccade (known as a noncancelled, or signal-respond, trial) or not (known as cancelled, or signal-inhibit, trials). Monkeys were reinforced for maintaining fixation on the stop signal for 600−700 ms after the stop signal appeared. A saccade to the target on a stop signal trial was incorrect, not reinforced, and resulted in a 1500 ms timeout. Stop signal delays ranged from 25 to 450 ms and were constant within an individual session. Behavioral and neurophysiolgical data from these monkeys has appeared in previous publications (Hanes et al., 1998; Ito et al., 2003; Paré and Hanes, 2003; Stuphorn et al., 2000). In addition to examining the

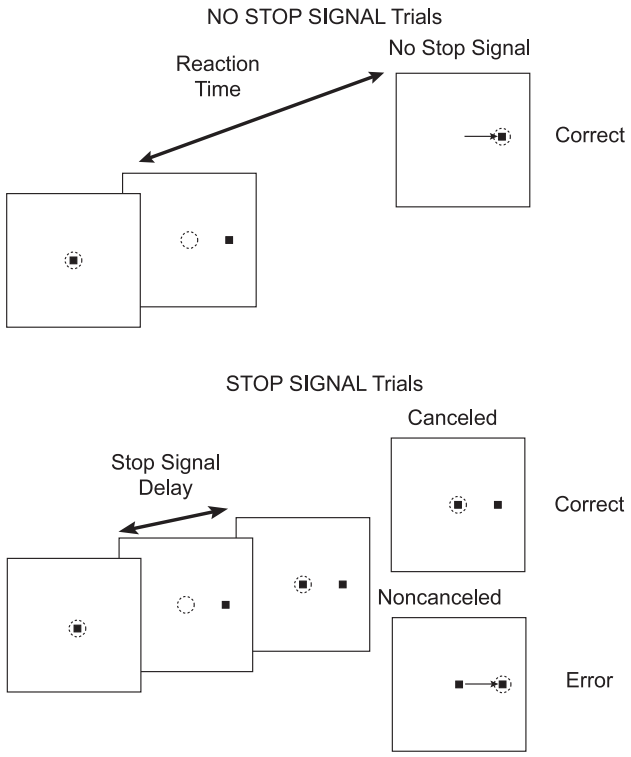

Figure 2.1: Trial displays for the countermanding task. Dotted circle indicates the focus of gaze at each interval; arrow, the saccade. All trials began with the presentation of a central fixation spot. After fixation of this spot for a variable interval, it disappeared. Simultaneously, a peripheral target appeared. During the trials in which the stop signal was not presented (no stop signal trials), producing a single saccade to the peripheral target is the correct response. During stop-signal trials, after a variable delay, the fixation spot reappears, which is the cue to inhibit/cancel movement initiation. During cancelled trials, fixation was maintained on the central spot for 700 ms. During noncancelled trials, a saccade to the peripheral target is produced.

effects of the local trial history on performance, we systematically manipulated the global proportion of stop signal trials. Behavioral data were obtained from monkey N performing a saccade countermanding when the proportion of stop signal trials was varied between 0.1 and 0.7 from session to session.

2.3.2 Human data collection

Human data were collected in two different laboratories from 7 subjects using similar paradigms. Two subjects were from Cambridge University and 5 were from Vanderbilt University. Each subject participated in a minimum of 8 (maximum of 11) sessions. All subjects reported having normal or corrected-to-normal vision. Informed consent was obtained before the experiment began. The Cambridge University Institutional Review Board and the Vanderbilt University Institutional Review Board approved the experimental procedures. The volume of data from 2 of the subjects was insufficient to provide sufficient statistical power for the comparisons examined below and could not contribute to all of the analyses.

Eye position was monitored using either the EyeLink II eye tracker (SR Research, Canada) at a sampling rate of 250 Hz with average gaze position error $< 0.5^\circ$, noise limited to $< 0.01^\circ$ RMS with pupil tracking, or an infrared scleral reflection oculometer (for details see Reddi and Carpenter 2000), sampled at 10msec intervals by a computer system, SPIC (Carpenter, 1994) that also controlled stimulus presentations. Saccades were detected online using conventional velocity and acceleration criteria. For the subjects tested at Vanderbilt University, the fixation and targets subtended 1.0° and were light gray (34 cd/m^2) on a darker gray (18 cd/m^2) background and the stop signal targets subtended 1.0° and were blue (34 cd/m^2), yellow (34 cd/m^2), or red (34 cd/m^2). For the subjects tested at Cambridge University, the fixation, targets, and stop signal targets subtended 0.22° and were yellow LEDs of luminance 160 cd/m^2 on a uniform background of 3 cd/m^2. The saccade stimuli were positioned

in a horizontal row at a spacing of 4.5° on each side of the mid-line; the LEDs were optically superimposed on a uniform background of 3 cd/m^2, and were therefore of very high contrast

All countermanding trials began with the presentation of a central fixation target which was accompanied by a warning tone for two subjects. After a random delay (500−1000 ms) the fixation stimulus went off and an eccentric target appeared at one of 4 random locations (45° from the cardinal positions) equidistant (8.5°) from the central fixation. Subjects were instructed to respond as quickly as possible to the appearance of the target. The remaining 30% of trials were stop signal trials during which the fixation point re-illuminated after a variable delay and indicated to the subject that the response they were instructed to make needed to be inhibited. Subjects were instructed that they would be unable to inhibit approximately half of the stop signal trials. The stop signal delays ranged from 25 to 275 ms in 50 ms steps or 50 to 120 ms in 10 ms steps. Each delay occurred with equal probability.

2.3.3 Primary data analysis

Behavioral data from the countermanding task include the distribution of response times on trials with no stop signal, the distribution of response times on noncancelled trials, and the probability of responding as a function of stop signal delay (SSD) (Logan et al., 1984). The inhibition function plots the probability of responding as a function of SSD; at the shortest SSD almost all saccades are cancelled, and at the longest SSD almost all saccades are not cancelled. To extract measures of the inhibition function, it was fit with a cumulative Weibull function of the form,

$W(t) = \gamma - (\gamma - \delta) * exp(-(t/\alpha)^{\beta})$, where t is the time after target presentation, β is the time at which the inhibition function reaches 64% of its maximum value, α is the slope, and γ and δ are the maximum and minimum of the inhibition function, respectively.

Saccades were detected using an algorithm that detects the first significantly elevated velocity ($> 30°$/s) using digital differentiation. Saccade initiation and termination were defined as the beginning and end of monotonic change in eye position before and after the high velocity gaze shift. Trials during which saccades were initiated after the target was presented while the monkey was fixating the central target and terminated on the target were classified as valid trials. For each valid trial, response time was the interval from target presentation to saccade initiation. The mean response time for each subject is the mean of session means and the standard error is the mean of the standard errors across sessions.

For each behavioral session, an estimate of SSRT was determined from the distribution of response times on no stop signal trials and the inhibition function. SSRT can be estimated in at least two ways (Logan et al., 1984). The first method of estimating the SSRT assumes that it is a random variable. Logan et al. (1984) showed that the mean SSRT is equal to the difference between the mean reaction time during no stop signal trials and the mean value of the inhibition function. The second method of estimating the SSRT assumes that it is constant. By this method, the SSRT is estimated by integrating the no stop signal saccade response time distribution, beginning at the time of target presentation, until the integral equals the proportion of noncancelled trials at that SSD. Detailed descriptions of these methods

have appeared previously (Hanes and Schall, 1995; Logan et al., 1984; Band et al., 2003a). In practice, these two methods rarely give identical values of SSRT because of noise and unavoidable measurement error. However, if enough trials are collected, then there is no reason to weight one method more than another (Band et al., 2003a). Therefore, we identified a single estimate of SSRT from the behavioral data collected during each physiological recording session by averaging the SSRT estimates derived from both methods (see Hanes et al. 1998; Kornylo et al. 2003).

2.3.4 Trial history analysis

Saccadic response times on no stop signal trials were sorted based on the trial history of stimuli and performance and were examined as a function of (1) the number of preceding no stop signal trials, (2) the number of preceding stop signal trials, and (3) whether the preceding stop signal trial was cancelled or noncancelled or was a no stop signal trial. Stop signal trials were sorted according to the same criteria and inhibition functions were derived for each subset of trials. Specifically, stop signal trials were first grouped as either (1) a function of the number of preceding stop signal trials (e.g., preceded by 1, 2, or 3 or more no stop trials) or (2) the type of preceding trial (i.e. cancelled, noncancelled, or no stop signal). Next, each subset of stop signal trials was then grouped by stop signal delay. Finally, inhibition functions were produced for each data subset by determining the proportion of noncancelled trials produced at each stop signal delay. A significant shift in the probability of responding was identified using maximum-likelihood fits of two nested general logistic regression models and by examining the significance of each factor through log-likelihood ratio

statistics (Dobson, 1990). Each inhibition function was fitted independently with a logistic regression function with stop signal delay and recent trial history as factors,

$$log[P/(1-P)] = b_0 + b_1 * SSD + b_2 * N_{No-Stoptrials}$$

$$log[P/(1-P)] = b_0 + b_1 * SSD + b_2 * N_{Stoptrials}$$

$$log[P/(1-P)] = b_0 + b_1 * SSD + b_2 * SST + b_3 * Correct$$

where **P** is the probability that a noncancelled saccade is produced on a stop signal trial, SSD is the value of stop signal delay, $\mathbf{N}_{No-Stoptrials}$ and $\mathbf{N}_{Stoptrials}$ are the number of preceding no stop signal and stop signal trials respectively. **SST** is a binary index where 1 or 0 represent the presence or absence of a stop signal on the preceding trial, respectively. **Correct** is a binary index where 1 and 0 represent if the preceding trial was correct or incorrect. For example, cancelled stop signal trials and no stop signal trials were assigned a value of 1, whereas noncancelled stop signal trials were assigned a value of 0. Finally, $\mathbf{b}_0$, $\mathbf{b}_1$, and $\mathbf{b}_2$ are coefficient estimates of the logistical fit. The residual sum of squares for each of the above model fits was compared to a logistic regression function with only stop signal delay as a factor,

$$log[P/(1-P)] = b_0 + b_1 * SSD$$

If the residual sum of squares of the model fit without the $\mathbf{b}_2$ and $\mathbf{b}_3$ coefficients was

significantly greater when compared with a chi-square distribution then the amplitude of shift was determined to be significantly different ($p < 0.05$).

2.4 Results

Data consisted of multiple saccade countermanding sessions performed by 6 monkeys and 7 human subjects. Five of the human subjects provided sufficient data for all analyses mentioned below; 2 subjects only contributed to some analyses.

2.4.1 Overall countermanding performance

The probability of responding on a stop signal trial for each monkey (Figure 2.2A) and human subject (Figure2.2B), regardless of the preceding trial events, was an increasing function of the stop signal delay. These inhibition functions are characteristic of performance in this task and demonstrate that all of the subjects were sensitive to the delivery of the stop signal.

Across all 7 human subjects, the mean no stop signal response time was 256 ± 2 ms and ranged from 232 ms to 270 ms (Figure 2.3, Table 2.2). The mean noncancelled response time on stop signal trials was 241 ± 5 and ranged from 191 to 293 ms. Across the 5 human subjects from whom we had sufficient data, noncancelled stop signal response times were significantly shorter than response time on no stop signal trials ($t(4) = -3.80$; $p = 0.01$). Likewise, across monkeys, the mean no stop signal reaction time was 273 ± 19 ms and ranged from 208 ms to 318 ms (Figure 2.3, Table 2.1). The mean noncancelled response time on stop signal trials was 241 ± 15 ms and ranged from 183 to 293 ms. Across monkeys, noncancelled stop signal

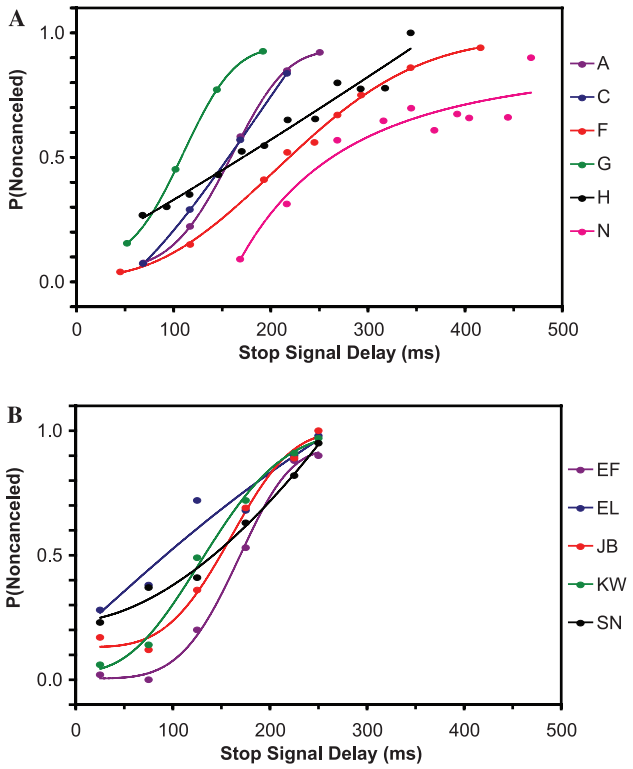

Figure 2.2: Overall inhibition functions from all stop signal trials across all sessions (A) for all monkeys and (B) for all human subjects. Data points are the probability of responding at each stop signal delay. The data from each individual is fit with a cumulative Weibull function.

Table 2.1: Response times of no stop signal trials, noncancelled trials, percent of stop signal trials that were noncancelled, and stop signal reaction time (SSRT) for each monkey.

Monkey	No-stop signal	Noncancelled	SSRTint	SSRTmean
A	256 ± 5	229 ± 7	94 ± 3	95 ± 2
C	246 ± 3	217 ± 6	98 ± 6	106 ± 5
F	282 ± 5	264 ± 7	103 ± 5	78 ± 5
G	208 ± 2	191 ± 3	95 ± 3	96 ± 2
H	252 ± 4	210 ± 8	114 ± 8	88 ± 4
N	318 ± 3	293 ± 6	98 ± 3	81 ± 1

Values are means ± SE. $SSRT_{int}$, stop signal reaction time determined using the method of integration. $SSRT_{mean}$, stop signal reaction time determined using the difference between the mean of the inhibition function and the mean of the response time distribution.

response times were significantly shorter than response time on no stop signal trials ($t(5) = -9.48$; $p < 0.01$). The orderly quality of the inhibition functions and shorter latency noncancelled response time compared to no stop signal response time indicates that both humans and monkeys were performing the task appropriately and justifies further analysis using the race model (Hanes et al., 1998; Hanes and Schall, 1995; Logan et al., 1984).

2.4.2 The effect of trial history on saccade latency on no stop signal trials

We measured the influence of preceding no stop signal trials on saccade latencies produced in trials with no stop signal (Figure 2.3). Trials were sorted into groups preceded by one, by two, or by three or more successive trials with no stop signal. Of the five human subjects with sufficient data, four demonstrated a decrease in no stop signal response time as the number of preceding no stop signal trials increased.

Table 2.2: Response times of no stop signal trials, noncancelled trials, percent of stop signal trials that were noncancelled, and stop signal reaction time (SSRT) for human subjects.

Subject	No-stop signal	Noncancelled	SSRTint	SSRTmean
SN	270 ± 2	282 ± 6	142	103
JB	251 ± 2	238 ± 4	150	82
KW	250 ± 2	225 ± 4	123	113
EF	276 ± 2	249 ± 5	120	114
EL	232 ± 3	211 ± 5	124	92

Values are means ± SE. SSRTint, stop signal reaction time determined using the method of integration. SSRTmean, stop signal reaction time determined using the difference between the mean of the inhibition function and the mean of the response time distribution.

Across these subjects, there was a significant effect of the number of preceding no stop trials on response time (F (2,4) = 5.30; $p = 0.03$). Similarly, four of six monkeys demonstrated a decrease in no stop signal response time as the number of preceding no stop signal trials increased. Across all monkeys, there was a significant effect of the number of preceding no stop trials on response time ($F(2,5) = 5.59$; $p = 0.02$).

We next measured the influence of preceding stop signal trials on the response time of trials with no stop signal (Figure 2.3). For five human subjects, no stop signal response time increased as the number of preceding stop signal trials increased. There was a significant effect of the number of preceding stop trials on response time ($F(2,4) = 19.49$; $p < 0.001$). For three of six monkeys, there was an increase in the no stop signal response time as the number of preceding stop signal trials increased. Across all monkeys, there was a significant effect of the number of preceding stop signal trials on response time ($F(2,5) = 4.27$; $p = 0.05$).

We next measured the influence of the preceding performance history on the re-

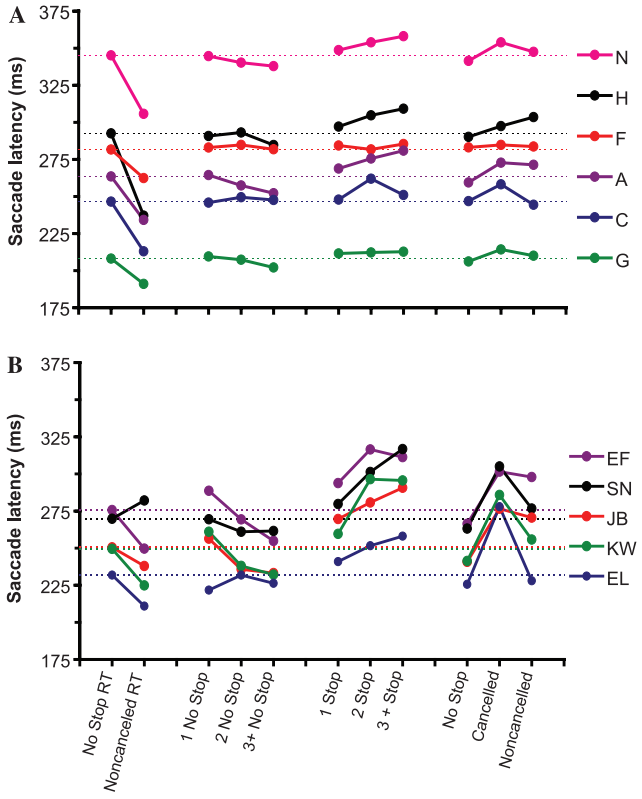

Figure 2.3: The influence of recent trial history on response time on no stop signal trials. The first columns represent the mean no stop signal response time and the mean noncancelled response time. All other columns represent the mean no stop signal reaction time for trials with the sequences of preceding trials indicated on the abscissa. The mean no stop signal reaction time for each subject is represented by the horizontal dotted line.

sponse time of trials with no stop signal. Stop signal trials could result in either correct cancelled (signal inhibit) or error noncancelled (signal respond) responses. No stop signal trials were sorted into groups preceded by no stop signal, by a stop signal that resulted in a cancelled saccade, and by a stop signal that resulted in a noncancelled saccade. Figure 2.3 displays the response time on no stop signal trials as a function of previous trial type.

Recall that we obtained sufficient data from 5 of 7 of the human subjects tested for statistical analysis. It is worth noting, however, that several trends were apparent in all seven subjects. First, no stop signal response time tended to be greater if immediately preceded by a cancelled stop trial than if preceded by a no stop trial. Second, response time on no stop signal trials were shorter if immediately preceded by a noncancelled stop signal trial than those preceded by a cancelled trial. Third, response times on no stop signal trials were greater following noncancelled trials compared to response time on no stop signal trials following no stop signal trials.

We next performed statistical analyses in the form of t-tests on the data from the five human subjects that we obtained sufficient data. We used a bonferroni corrected alpha level of 0.02 to determine significance. No stop signal response time was significantly greater following cancelled trials compared to no stop signal response time following no stop signal trials ($t(4) = -14.04$; $p < 0.01$). There was no significant difference in no stop signal response time between trials preceded by a noncancelled trial or a no stop signal trial ($t(4) = -3.34$; $p = 0.03$) or between trials preceded by a noncancelled trial or a canceled trial ($t(4) = 2.78$; $p = 0.05$).

Data obtained from the six monkeys in this task provided comparable results to

the human data. No stop signal response time was significantly greater following cancelled trial compared to no stop signal response time following no stop signal trials ($t(5) = -5.05$; $p < 0.01$). There were no significant differences in no stop signal response times between trials preceded by a cancelled trial or a no stop signal trial, ($t(5) = 1.20$; $p = 0.29$) or between trials preceded by a noncancelled trial or a canceled trial ($t(5) = -2.20$; $p = 0.08$).

2.4.3 Time course of the effect of trial history

The large volume of data collected from the monkeys allowed for an analysis of the time course of the effect of trial history on response times. The moving average of response time was calculated as the mean no stop signal response time for rewarded trials in the preceding 40 trials for each of 516 sessions (Figure 2.4). Likewise, the proportion of stop signal trials was determined from the fraction of stop signal trials in the same 40-trial window. Previous studies have demonstrated that neuronal activity and behavior in recent trials are weighted more than earlier trials (e.g., Cho et al. 2002; Hasegawa et al. 2000; Sugrue et al. 2004). Weighted moving averages were calculated using an exponentially decaying function with time constants of 5 and 20 trials. The cross-correlation sequence of the normalized response time on no stop signal trials and the normalized recent fraction of stop signal trials was determined. For example, if the peak of the cross-correlation sequence occurs at a lag of -10 trials, this implies a response time correlation with stop signal trials that occurs 10 trials in the past. A significant peak correlation was defined as a correlation that exceeded the 99% confidence interval (Chatfield, 1975) that occurred in the trial interval between

-15 and +5 trials. This is because correlations outside this window are most likely due to statistical fluctuations in the data.

2.4.4 The effect of trial history on canceling

To determine if the recent fraction of stop signal trials influences the probability of responding, a logistic regression with factors stop signal delay and the recent trial history was performed. The results are plotted in Figures 2.5,2.6,2.7, and 2.8 . The probability of responding significantly increased for two of six monkeys (monkeys A and G) as the number of preceding no stop signal trials increased. The probability of responding significantly decreased for two of six monkeys (monkeys G and F) as the number of preceding stop signal trials increased. For three of six monkeys (monkeys A, G, and N), the probability of responding was greatest if preceded by a no stop signal trial, less if preceded by a noncancelled trial, and least if stop signal trials were preceded by cancelled trials.

Similar to the analysis on the data obtained from monkeys, stop signal trials for human subjects were sorted based on whether the immediately preceding trial was a no stop signal trial or a stop signal trial. For one of five human subjects (subject KW), the probability of responding on stop signal trials was less if stop signal trials were immediately preceded by a stop signal trial compared to stop signal trials immediately preceded by no stop signal trials. In addition, the probability of responding for subject KW was greatest if preceded by a no stop signal trial, less if preceded by a noncancelled trial, and least if stop signal trials were preceded cancelled trials. There was no discernable pattern in the inhibition functions for the remaining

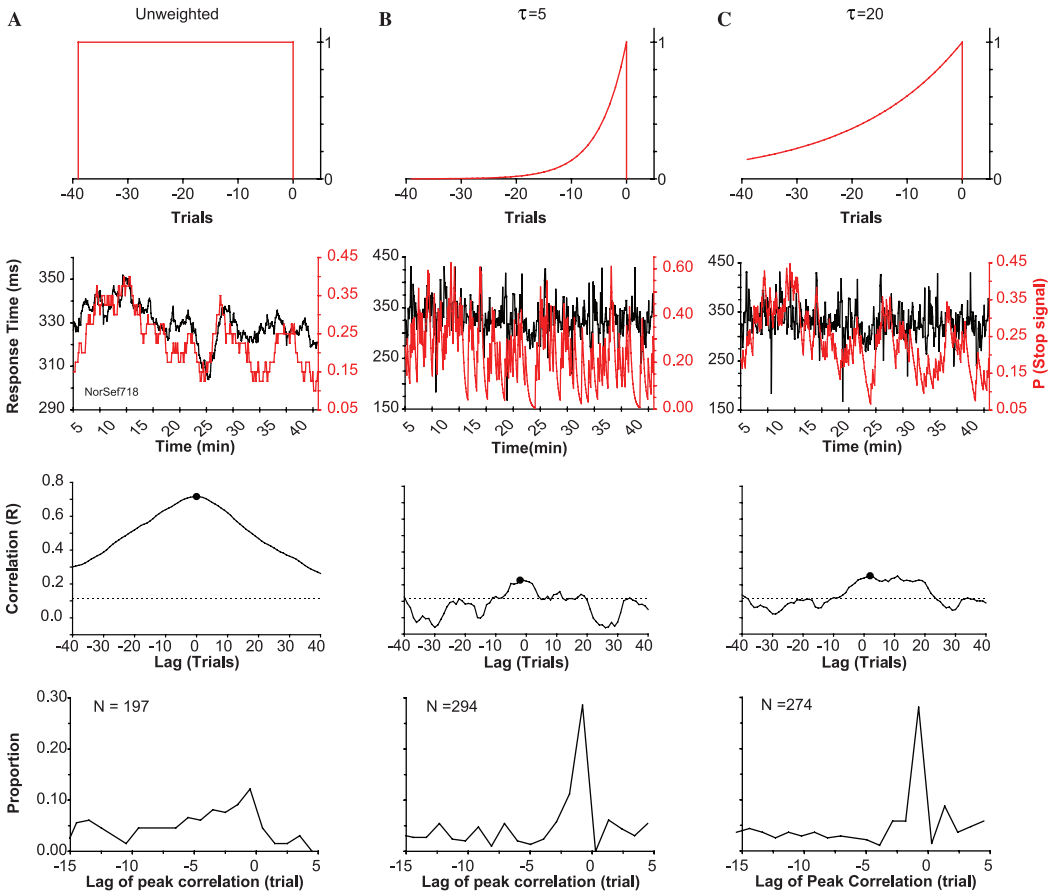

Figure 2.4: Cross-correlation between moving averages of the fraction of stop signal trials and response time in the preceding 40 trials. The first, second, and third columns represent unweighted (A) and weighted means with time constants, t, of 5 (B) and 20 (C) trials, respectively. The top row of figures are schematics of the functions used to convolve the response times and stop fractions. The second row provides an example of the temporal correlation between the local fraction of stop signal trials and response time for a representative countermanding session. The third row of figures are plots of correlation coefficient of stop fraction with response time shifted the number of trials at that point on the ordinate. The circle is the maximum correlation coefficient. The dashed line defines the two-tailed 99% confidence limit. The bottom row of figures are the distributions of the lags at which the cross correlation between moving averages of response time and the fraction of stop signal trials was maximized. N in each figure represents the number of countermanding sessions with significant correlations.

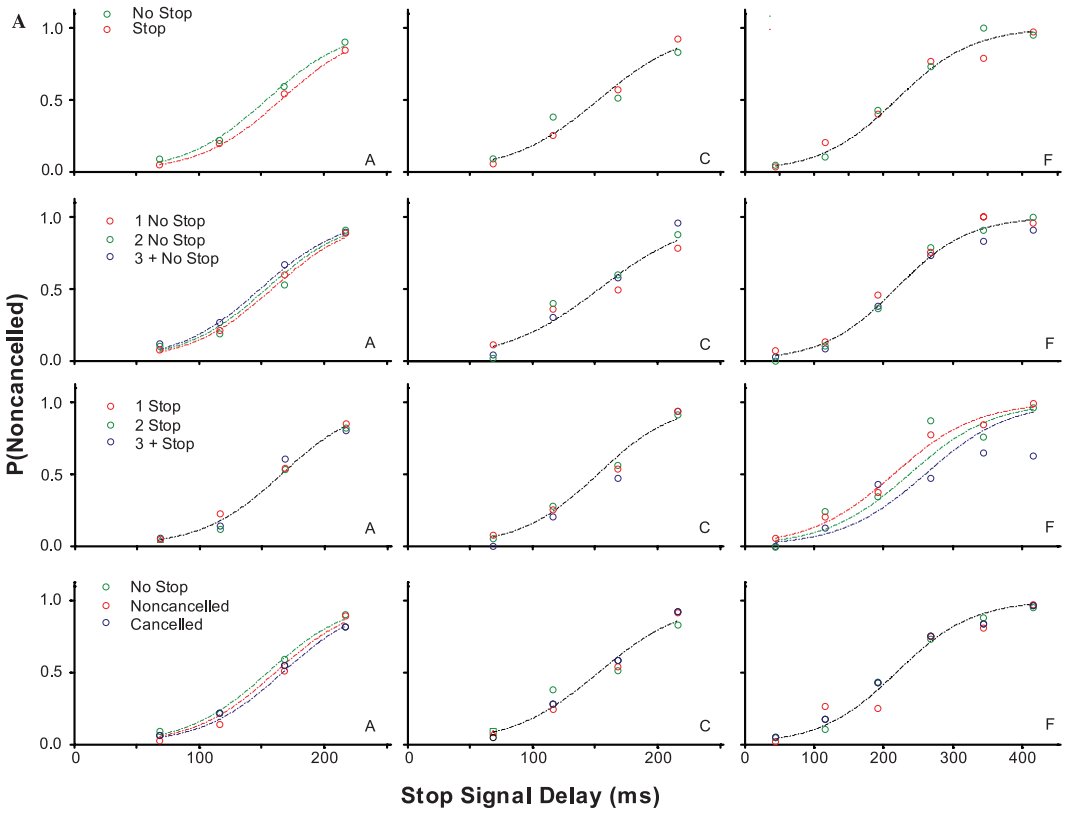

Figure 2.5: The effect of recent trial history on the probability of responding. Each column is the data from monkeys A, C, and F. Inhibition functions from stop signal trials preceded by specific sequences of trials fit with logistical models with stop signal delays and the local trial history as factors, log [P/(1 - P)] = b0 + b1 * SSD + b2 * TRIAL HISTORY and only stop signal delay as a factor, log [P/(1 - P)] = b0 + b1 * SSD. A significant effect of trial history is indicated by a fit plotted for each inhibition function. No effect of trial history is indicated by a single fit. A leftward shift in the fit indicates a lower probability of responding. Each row of plots is the probability of responding when stop signal trials were immediately preceded by a no stop signal trial versus a stop signal trial (1st row), preceded by 1, 2, or 3 or more no stop signal trials (2nd row), preceded by 1, 2, or 3 or more stop signal trials (3rd row), immediately precede by a no stop signal trial, a cancelled stop signal trial, or a noncancelled stop signal trial (3rd row).

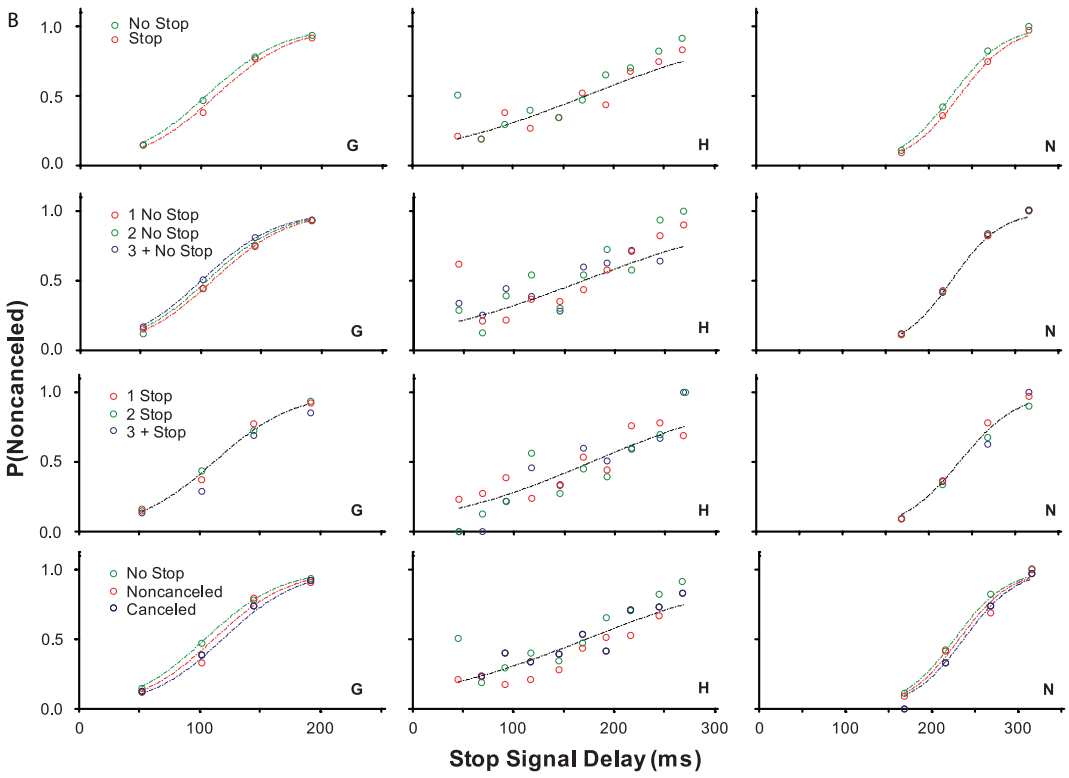

Figure 2.6: The effect of recent trial history on the probability of responding. Each column is the data from monkeys G, H, and N. Conventions the same as Figure 2.5.

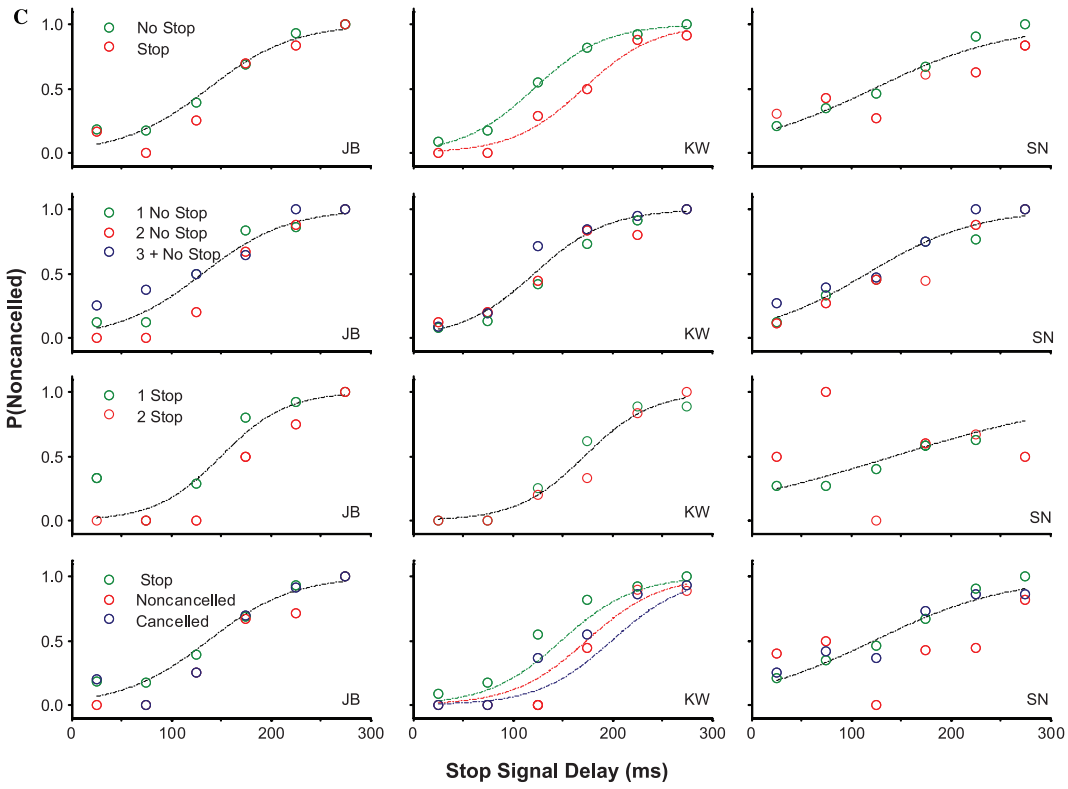

Figure 2.7: The effect of recent trial history on the probability of responding. Each column is the data from human subjects EF and EL. Conventions the same as Figure 2.5.

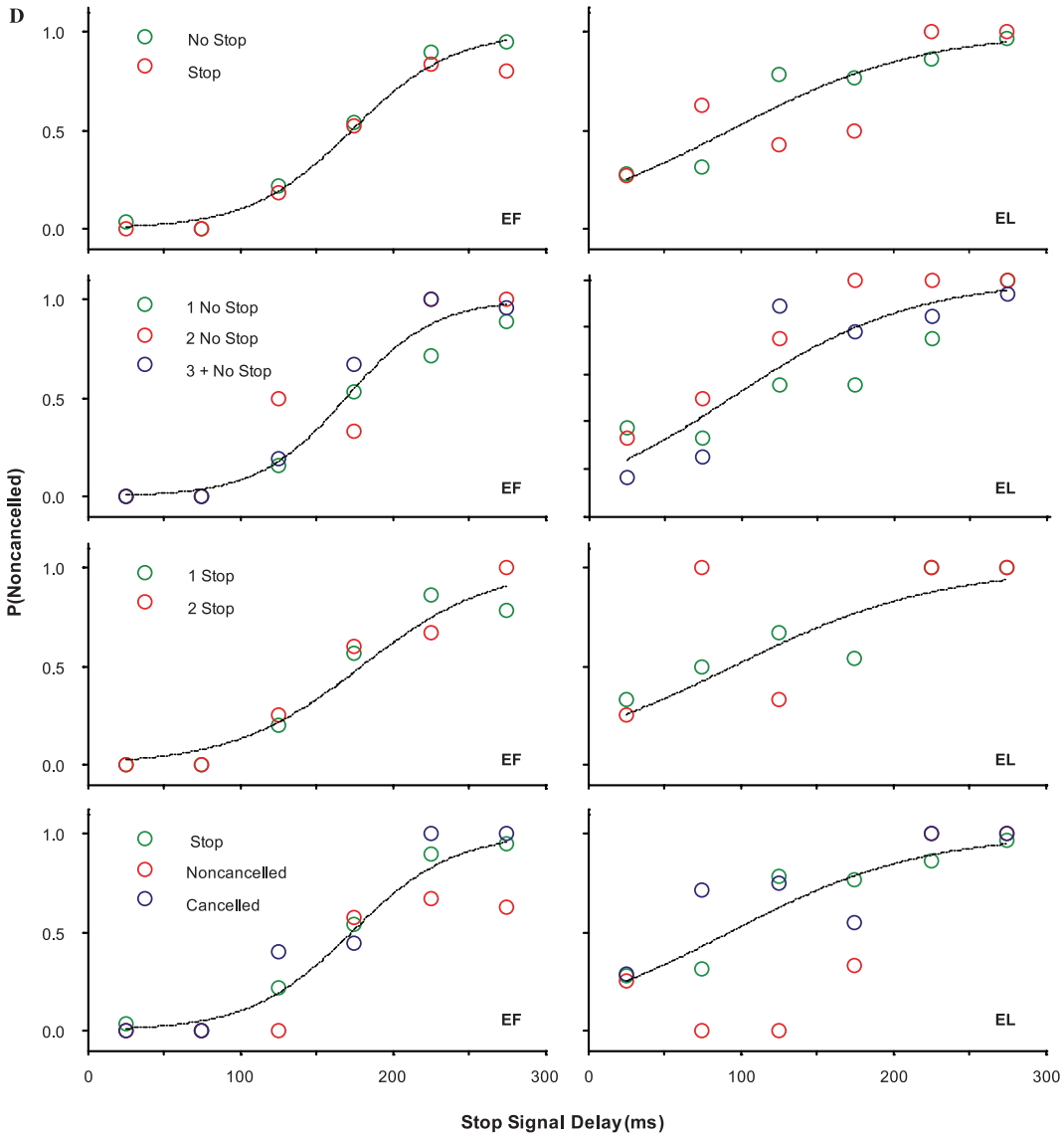

Figure 2.8: The effect of recent trial history on the probability of responding. Each column is the data from human subjects JB, KW, and SN. Conventions the same as Figure 2.5.

four human subjects.

2.4.5 The effect of the global stop signal probability on countermanding performance

In addition to local trial history, variation in stimulus and response history on a longer time scale have also been demonstrated to affect countermanding performance (Logan, 1981; Logan and Burkell, 1986; Ramautar et al., 2004). To determine if the global proportion of stop signal trials affects both the response time and the probability of responding, behavioral data were obtained from one monkey while systematically varying the fraction of stop signal trials between 0.1 and 0.7 between sessions for each day of testing. Monkey N performed 22 sessions of saccade countermanding over the course of 7 days. Significant shifts in response time on no stop signal trials in response to changes in the global stop fraction occurred on all 7 days (Kruskal-Wallis test $p < 0.05$) (Figure 6B). In 5 of 7 days, the probability of responding decreased significantly with increasing stop signal fraction ($p < 0.05$) (Figure 6A). A linear regression of the change in response time on the change in stop fraction from session to session revealed a significant correlation ($R^2 = 0.43$, $p < 0.05$).

2.5 Discussion

2.5.1 Summary of results and relation to previous results

The results of the present analysis of trial and performance history in humans and macaque monkeys performing a saccade countermanding task revealed significant, systematic shifts in response times and smaller idiosyncratic changes in the probability of responding on trials with a stop signal. Overall, response times on trials with no

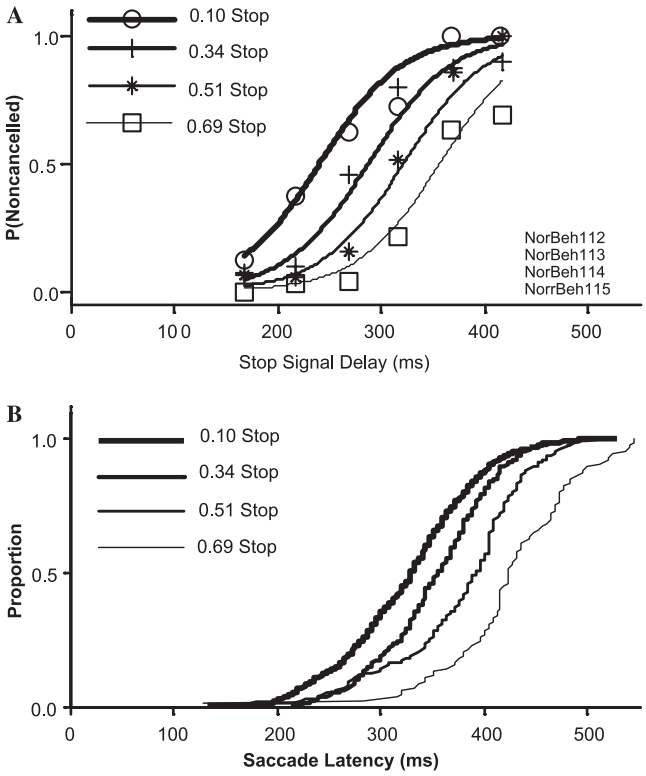

Figure 2.9: The effect of varying the global probability of a stop signal trials on the probability of responding and response time on no stop signal trials for monkey N. (A) The probability of responding was fit with logistical models with stop signal delays and the global stop ratio as factors, log [P/(1 - P)] = b0 + b1 * SSD + b2 * STOP RATIO, and with only the stop signal delay as a factor, log [P/(1 - P)] = b0 + b1 * SSD. A significant effect of trial history is indicated by a fit plotted for each inhibition function. Leftward shifts in the curves indicate a lower probability of responding. (B) Cumulative density functions of no stop signal reaction times as a function of stop ratio. The distributions are significantly different (Kruskal-Wallais test, $p < 0.05$).

stop signal decreased significantly with the number of preceding no stop signal trials. Conversely, a significant increase in response time on no stop signal trials with the number of preceding stop trials was observed for the human subjects, but not for the monkeys. Both human subjects and monkeys produced longer saccade latencies on no stop signal trials following correct cancelled trials, but not following error noncancelled trials. In other words, we found no post-error slowing in the saccade countermanding task for humans or monkeys. The response time adjustments on no stop signal trials were driven mainly by the immediately preceding stop signal trial. In contrast to these adjustments of response times, the probability of responding on stop signal trials was only weakly affected by trial history unless large changes in the fraction of stop trials occurred within a session.

Our results replicate and extend those from previous countermanding studies. Specifically, the overall delay of response times following stop signal trials has been reported for saccades (Cabel et al., 2000; Kornylo et al., 2003) and manual responses (Rieger and Gauggel, 1999; Schachar et al., 2004). Furthermore, the findings that saccade latencies on trials with no stop signal are shorter following no stop signal trials than following stop signal trials and that saccade latencies on trials with no stop signal are elevated more following cancelled trials than following noncancelled trials replicates previous reports (Cabel et al., 2000; Kornylo et al., 2003). However, Curtis et al. (2005) report the opposite – saccade latencies following stop signal trials were shorter than saccade latencies following no stop trials, and saccade latencies were shorter following cancelled trials than saccade latencies following noncancelled trials. However, a major difference in this the Curtis study was the inclusion of catch

trials in which no saccade target was presented and the subjects were only required to maintain fixation on the central target for the duration of the trial. Therefore a direct comparison between these data may not be valid.

The absence of elevated saccade latencies following noncancelled errors in the saccade countermanding task is inconsistent with previous observations of delayed responses following errors in choice response time tasks (e.g., Rabbitt 1966b,a; Rabbitt and Phillips 1967; Laming 1979; for review see Rabbitt 1977. The absence of post-error slowing in our data can be explained a number of ways. First, we may not have obtained enough data to reveal the effect. This is unlikely, though, because we analyzed a large quantity of data in this study from six monkeys and seven human subjects across three laboratories. This amount of data should have revealed a post-error slowing effect if such an effect was present. Second, countermanding errors may have a different salience or valence than errors produced in choice response time experiments. For the monkeys, a noncancelled saccade to the target resulted in the omission of reinforcement and sometimes a prolonged intertrial interval. We believe that these conditions are clear, unambiguous cues regarding the outcome of the trial. For the human subjects, the difference in instructions for choice response time tasks versus countermanding may also explain the absence of post-error slowing. In response time tasks, subjects are typically instructed not to make errors, thus errors might be perceived as a significant event. Conversely, human countermanding subjects were instructed that they would be unable to inhibit approximately half of the stop signal trials and not to worry if they were unable to successfully inhibit responses. In addition, there was no error feedback at the conclusion of each trial.

Thus, human subjects were dependent on internal performance monitoring to detect whether errors had been produced and, because of the instructions, may have been less inclined to monitor and correct errors. In summary, by design, errors in the stop signal task are common and so may not engage executive control to delay responding as much as might errors in other tasks. Third, a difference between monitoring saccadic and manual errors may result in a difference in how and when the error signal is used to adapt the behavior. In fact, delayed manual response times following noncancelled and cancelled stop signal trials have been reported in choice tasks (Rieger and Gauggel, 1999; Schachar et al., 2004) and reaching movements (Mirabella et al., 2006). Preliminary work from this lab indicates an absence of post-error slowing for noncancelled manual joystick movements as well (Boucher et al., 2007a). Clearly, further work is required to determine if monitoring manual and saccade countermanding errors differ.

The response conflict monitoring hypothesis may provide a parsimonious explanation for the increase in response times following cancelled trials and the absence of post-error slowing (Botvinick et al., 2001). In this model, conflict is defined as the coactivation of mutually incompatible response processes. The countermanding task creates an incompatibility between the process that initiates the movement (GO process) and the process that inhibits the movement (STOP process). Several lines of evidence indicate that for saccade production, the GO process can be identified with the activity of presaccadic movement neurons in the frontal eye field and superior colliculus; while the STOP process can be identified with the activity of fixation neurons (reviewed by Schall 2004;see also Boucher et al. 2007b). Neurophysiological

recordings in monkeys performing the saccade stop signal task have demonstrated that movement and fixation neurons are maximally coactive during cancelled trials but are not coactive in noncancelled trials or no stop signal trials (Hanes et al., 1998; Paré and Hanes, 2003). According to the proposition that conflict monitoring serves to translate the occurrence of conflict into compensatory adjustments in control, the greater coactivation on cancelled trials should result in greater slowing of saccades on the subsequent trials which is just what we observed.

Response time adjustments are not unique to the countermanding task. Previous studies, using other tasks, have also found that macaque monkeys are sensitive to sequential dependencies (Dorris et al. 1999, 2000; Procyk et al. 2000; see also Bichot and Schall 1999; reviewed by Fecteau and Munoz 2003). In this data set, the sensitivity of response time to stimulus history was revealed further through the strong correlation observed between a running average of response latency and a running average of the fluctuating fraction of stop signal trials. However, the time scale of this relation appears to be relatively short. We found that the correlation between response time and the fraction of stop signal trials was largest for the immediately preceding trial, and the correlation was absent across entire sessions. These adjustments in response time as a result of preceding trial coincided with subtle and variable effects of stimulus or performance history on the probability of responding. Macaque monkeys and humans subjects were sensitive to both stimulus history (stop signal trial versus no stop signal trial) and performance history (cancelled saccade versus noncancelled saccade).

2.5.2 Sequential effects and the race model

The trial history effects reported here and in previous studies cannot be explained by the original race model of stop signal performance (Logan et al., 1984). As originally conceived, the race model accounts for the outcome of an individual trial by drawing a GO process finish time and a STOP process finish time from stochastically independent distributions and determining which process finished first. Thus, the original formulation of the race model has no memory. Accordingly, some have suggested that the occasional occurrence of longer latency responses on short stop signal delay trials constitutes a violation of the assumption that the GO and STOP processes are independent (e.g., Özyurt et al. 2003; Colonius et al. 2001). However, independence within and across trials must be distinguished. It seems clear that when stop signal trials occur, subjects adopt a more cautious strategy by slowing responses on subsequent trials. However, such deliberate slowing does not necessarily violate the fundamental premise of the race model that the GO and STOP finish times are stochastically independent. In fact, when subjects do not delay responses systematically, then their performance does not conform to the predictions of the race model (Özyurt et al., 2003).

It is not hard to conceive of how the original race model could be extended to account for sequential effects. According to the race model, response time adjustments and changes in the probability of responding must be produced via a modification in the finishing times of the GO and STOP processes. For instance, decreasing the finish times of the GO process on successive trials biases the outcome of the race

toward producing a movement. Therefore, following a sequence of no stop signal trials when saccade latency is reduced, the probability of canceling the movement is reduced on subsequent stop signal trials. Conversely, increasing the finish times of the GO process on successive trials biases the outcome of the race toward inhibiting a movement. Therefore, following a sequence of stop signal trials when saccade latency is increased, the probability of canceling the movement is increased on subsequent stop signal trials.

What mechanisms could be the basis for these effects? Two non-exclusive alternatives will be considered here. On the one hand, the adjustments in performance could come about through processes intrinsic to the mechanism that produces the movement. On the other hand, the adjustments could require intervention of a process extrinsic to the mechanism that produces the movement.

2.5.3 Intrinsic adjustment mechanism

It is possible that the adjustments of performance due to trial history occur through changes in the mechanisms that produce the response. For example, adjustments of response time according to stimulus history can be accounted for within the framework of the LATER model (Carpenter and Williams, 1995; Reddi and Carpenter, 2000; Carpenter, 2001). According to this model, movements are initiated when an accumulating signal reaches a fixed criterion or threshold. Because the threshold does not vary, the stochastic variability in response time originates in randomness of the rate of growth or the starting level of the processes. However, changes in the probability of responding and response time can also occur through changes in the

starting level or criterion of the accumulator (Reddi and Carpenter, 2000; Carpenter, 2001). In other words, the starting levels for the racing signals - their handicaps, in effect - may be influenced by prior likelihoods. This was examined, and confirmed by Carpenter and Williams (1995) for a simple reaction time task in which no stop signals were presented. Alterations in expectation induced by changes in the prior probabilities of the targets resulted in changes in mean latencies and in the distribution of latencies that could be quantitatively predicted by the LATER model. Recently, studies have demonstrated the effect of the immediately prior stimulus history in a way that can be explained by the effects of stimulus history on target expectations (Carpenter, 2001). It is not difficult to imagine a similar mechanism at work in the countermanding task. A local increase in the frequency of stop trials may result in an elevated starting level for the STOP process. This would lead to a decreased probability of responding and a reduced SSRT. However, this could not explain the observed increased response times on no stop signal trials when preceded by a run of stop signal trials. It may be that another factor is at work in addition to prior probability information, namely a change in the criterion level at which the racing signals trigger a response. In simple saccadic response time tasks, instructions to the subject to make fewer errors appear to result in an elevation of this criterion or threshold level (Reddi and Carpenter, 2000). Thus, it seems clear that the presence of both cancelled and noncancelled stop signal trials could result in a more cautious setting for the criterion level.

The neural mechanisms that control the initiation of saccadic eye movements can also offer some insights (Schall and Thompson, 1999; Munoz et al., 2000; Stuphorn and

Schall, 2002). The architecture of a stochastic growth to a fixed threshold corresponds to the pattern of neural activity in the frontal eye field and superior colliculus that produces saccades (Hanes and Schall 1996; see also Sparks et al. 1976; Dorris et al. 1997; Dorris and Munoz 1998). However, the absolute level of the triggering threshold might vary with the context of the task (Everling et al., 1999; Everling and Munoz, 2000). Nevertheless, the activity of presaccadic movement and fixation neurons in the frontal eye field and superior colliculus modulate in a manner sufficient to control whether or not saccades are produced in the countermanding task (Hanes et al., 1998; Paré and Hanes, 2003). Furthermore, a new interactive race model shows that the GO and the STOP processes of the race model can be instantiated by units with properties corresponding to movement and fixation neurons (Boucher et al., 2007b). Further evidence that the adjustments of performance observed in this study may be mediated by these neurons is derived from observations of the covariation of movement and fixation neuron activity in the superior colliculus with changes in saccade probability and latency (Dorris and Munoz, 1998; Dorris et al., 1997, 2000). For example, the level of activation of movement neurons before a stimulus appears is correlated with the latency of the saccade to the stimulus. Thus, these data indicate that changes in the processes that produce saccades can account for changes in the probability and latency of the movement.

One drawback of considering data related to the intrinsic mechanisms of response time adjustments is that these data do not reveal how such changes in activity come about. We turn our attention next to extrinsic adjustment mechanisms, which may provide such an explanation.

2.5.4 Extrinsic adjustment mechanism

Many have suggested that executive control over the perception, selection, and production systems is a central component of human cognition (e.g. Logan 1985; Norman and Sallice 1986; Allport et al. 1994; Baddeley and Della Sala 1996; Logan and Gordon 2001; Repovs and Baddeley 2006). When the environment is ambiguous or presents competing demands, or the mapping of stimulus onto response is complex or contrary to habit — thereby making performance prone to errors — this executive control system is called into action. The original behavioral evidence for an executive control system included adjustments in response time following errors (e.g. Rabbitt 1966b,a; Rabbitt and Phillips 1967; Laming 1979).

Physiological evidence for a monitoring system in the medial frontal lobe has also been obtained. Event-related potential and neuroimaging studies have shown that activation in the medial frontal lobe, centered in anterior cingulate cortex (ACC) is associated with registering the production of errors or conflicting processes, and the need for adjusted control of behavior (reviewed by van Veen and Carter 2002; Nieuwenhuis et al. 2004; Ridderinkhof et al. 2004). Evidence consistent with this general hypothesis has been obtained in neurophysiological recordings from the supplementary eye field (SEF) and ACC in monkeys performing the countermanding task (Stuphorn et al., 2000; Ito et al., 2003).

Consistent with the ERP and neuroimaging literature, neurons in SEF do not generate signals sufficient to control gaze according to the logic of the countermanding paradigm (see Schall et al. 2002). Instead, distinct groups of neurons in SEF and ACC

are active either after errors, after successful withholding of a partially prepared movement, or in association with reinforcement (Stuphorn et al., 2000; Ito et al., 2003). In addition, Curtis et al. (2005) observed SEF activation that covaried with response time adjustments. Thus, a part of the brain that is not directly responsible for producing movements of the eyes, appears to produce signals that are the basis of models of self-monitoring and control. Altogether, the evidence indicates that SEF activity reflects performance monitoring, but does it play a role in response time adjustments? Recent evidence indicates that subthreshold, intracortical electrical stimulation of SEF reduces the probability of countermanding errors by increasing saccade latency (Stuphorn and Schall, 2006). Thus, these signals are capable of exerting influence on behavior.

2.6 Conclusions

The neural basis of the self-control of eye movements has been investigated with increasing precision due in large part to improved behavioral testing procedures and theoretical perspectives. We have examined the relationship between such control and predispositions derived from the responses produced on previous trials. The purpose of this retrospective analysis was to determine whether such contextual effects were present in human and macaque monkey subjects performing the countermanding task, and if so, to verify if current models of stop signal performance could explain such behavioral adjustments. The results provide strong evidence that performance in a saccade countermanding task is influenced by trial history and indicate that the Logan et al. (1984) race model of countermanding will need to be extended to explain

these results. Preliminary results demonstrate that history-dependent modulation of the finish time of the GO process can account for these effects (Boucher et al., 2007b).

CHAPTER III

PERFORMANCE MONITORING LOCAL FIELD POTENTIALS IN THE MEDIAL FRONTAL CORTEX OF PRIMATES: ANTERIOR CINGULATE CORTEX

3.1 Abstract

We describe intracranial local field potentials (LFP) recorded in the anterior cingulate cortex (ACC) of macaque monkeys performing a saccade countermanding task. The most prominent feature at ∼70% of sites was greater negative polarity after errors than after rewarded correct trials. This negative polarity was also evoked in unrewarded correct trials. The LFP evoked by the visual target was much less polarized, and the weak presaccadic modulation was insufficient to control the initiation of saccades. When saccades were cancelled, LFP modulation decreased slightly with the magnitude of response conflict that corresponds to the coactivation of gaze-shifting and -holding neurons estimated from the probability of canceling. However, response time adjustments on subsequent trials were not correlated with LFP polarity on individual trials. The results provide clear evidence that error- and feedback-related, but not conflict-related, signals are carried by the LFP in the macaque ACC. Finding performance monitoring field potentials in the ACC of macaque monkeys establishes a bridge between event-related potential and functional brain-imaging studies in humans and neurophysiology studies in non-human primates.[1]

[1]This chapter was published as Emeric EE, Brown JW, Leslie M, Pouget P, Stuphorn V, Schall JD.Performance monitoring local field potentials in the medial frontal cortex of primates: anterior cingulate cortex.*J Neurophysiol* 2008:99, 759-772

3.2 Introduction

Human errors in reaction time tasks are associated with the error-related negativity (referred to as ERN or Ne) and a later positive deflection (Pe) (e.g., Falkenstein et al. 1991; Gehring et al. 1993). The ERN has a frontocentral distribution over the scalp and peaks ∼100 ms after the incorrect response in choice-reaction time tasks or the uninhibited response on no-go trials (Scheffers et al., 1996). A dipole for the ERN can be located in the anterior cingulate cortex (ACC) (e.g., Dehaene et al. 1994; Miltner et al. 1997; van Veen and Carter 2002). At least three hypotheses have been proposed to explain this signal and the function it performs.

First, the error-monitoring hypothesis proposes that the ERN/Ne reflects a comparison between the representations of the overt error response and the correct response (Falkenstein et al., 1991; Gehring et al., 1993), a function comparable to other midline negativities signaling mismatch (Näätänen et al., 1978) and the N400 (Kutas and Hillyard, 1984). However, the presence of frontocentral negativities during correct trials, albeit of smaller amplitude (e.g., Falkenstein et al. 2000; Vidal et al. 2000) is difficult for the error-monitoring hypothesis to account for (Coles et al., 2001).

Second, the reinforcement-feedback hypothesis proposes that this frontocentral negativity is elicited by feedback indicating error, loss, or punishment (Gehring and Willoughby, 2002b; Miltner et al., 1997). In particular, Holroyd et al. (2002) hypothesize that the mesencephalic dopamine system conveys a reinforcement learning signal to the frontal cortex when participants commit errors. According to this model, the ERN is generated because the inhibitory influence of the dopaminergic innervation

in the ACC is modulated, fine-tuning the ACC to enable more appropriate choices in the subsequent trial.

Third, the conflict-monitoring hypothesis proposes that control is recruited based on the coactivation of mutually incompatible response processes (Botvinick et al., 2001, 2004). This hypothesis was formulated originally based on fMRI evidence for a conflict-monitoring function of the ACC (Botvinick et al., 1999; Carter et al., 1998, 1999). Subsequent work suggested that response conflict was also reflected in the frontocentral N2 event-related potential component (Yeung et al., 2004), which is similar to the ERN and can be localized to an ACC-generator comparable to that of the ERN (Kopp et al., 1996).

Numerous experiments have sought to test the error-monitoring, reinforcement-feedback, and conflict-monitoring hypotheses (reviewed by Botvinick et al. 2004; Ridderinkhof et al. 2004; van Veen and Carter 2006). This extensive literature can be summarized with the statement that each hypothesis remains plausible, and none can be excluded entirely. One reason for this lack of conceptual resolution is the low spatial or temporal resolution of event related potentials (ERP) and functional magnetic resonance imaging (fMRI) measures. The opportunity to carry out invasive studies in non-human primates can contribute to resolving among these alternative hypotheses. In fact, in monkeys performing a saccade stop signal task, single-unit activity signaling errors, reinforcement, and response conflict has been observed in the supplementary eye field (SEF) (Stuphorn et al., 2000). Similarly, single-unit activity signaling errors and reinforcement, but not response conflict, has been observed in the dorsal bank of the ACC (Ito et al., 2003). These results are consistent with other re-

sults showing SEF and ACC unit modulation correlated with monitoring performance in macaque monkeys performing other tasks (Amiez et al., 2006; Isomura et al., 2003; Koyama et al., 2000, 2001; Nakamura et al., 2005; Niki and Watanabe, 1979; Procyk and Joseph, 2001; Procyk et al., 2000; Shidara and Richmond, 2002, 2005). However, scalp potentials are the summation of intracranial local field potentials and not unit discharges (reviewed by Nunez and Srinivasan 2005). Therefore drawing conclusions based on converging evidence from single unit studies in non-human primates and ERP or fMRI studies in humans entails several uncertain inferences.

The goal of this study was to lay the first planks in a bridge between monkey single-unit data and human ERP and fMRI data by determining whether local field potentials (LFPs) signaling error, reinforcement, or conflict are observed in the ACC of macaque monkeys performing a saccade stop signal (or countermanding) task. This task requires subjects to produce speeded responses that countermand, or cancel, a partially prepared movement to a target when a stop signal is presented at various stages of preparation (Hanes and Schall, 1995; Logan, 1994; Logan et al., 1984). A saccade version of the stop signal task has been used to examine the role of the frontal eye field and superior colliculus in controlling the initiation of saccades (Hanes et al., 1998; Paré and Hanes, 2003; Brown et al., 2008) and the role of the SEF and the ACC in monitoring performance (Ito et al., 2003; Stuphorn et al., 2000) but not controlling saccade initiation (Stuphorn and Schall, 2006).

The present study reports the characteristics of LFPs that were recorded simultaneously with single units in the ACC of monkeys performing the saccade stop signal task. We determined whether intracerebral negativities (like the ERN/Ne) and posi-

tivities (like the Pe) occur in the ACC when monkeys made countermanding errors. We also investigated whether the premovement LFPs were modulated in a manner sufficient to control saccade initiation. Finally, we determined whether LFPs in the ACC were modulated in a manner consistent with signaling response conflict. The results provide clear evidence that LFP in the ACC do not contribute to saccade initiation and that error- and feedback-related, but not conflict-related, LFP modulation occur in the ACC of macaque monkeys.

3.3 Methods

Data were collected from two male bonnet monkeys (*Macaca radiata*: 8-10 kg) that were cared for in accordance with U. S. Department of Agriculture and Public Health Service Policy on the humane care and use of laboratory animals. Each animal was tested for ∼4 h/day, 5 day/wk. During testing, water or fruit juice was given as positive reinforcement. Access to water in the home cage was controlled and monitored. Fluids were supplemented as needed. Detailed descriptions of all surgical procedures, electrophysiological techniques behavioral training, and tasks have appeared previously (Hanes and Schall, 1995; Hanes et al., 1998).

The experiments were under computer control to present stimuli, record eye movements, and deliver liquid reinforcement. Stimuli were presented on a video monitor (48 x 48°) using computer-controlled raster graphics (Peritek VCH-Q, 512 x 512 resolution or TEMPO Videosync 1280 x 1040 resolution). The fixation spot subtended 0.37° of visual angle, and the target stimuli subtended from 0.3 to 3° of visual angle, depending on their eccentricity and had a luminance of 10 or 30 cd/m^2 on a 1 cd/m^2

background. Eye position was monitored via a scleral search coil or a video-based infrared eye tracker (ASL, Bedford, MA) while monkeys were head-restrained and seated in an enclosed chair within a magnetic field. Saccades were detected using a computer algorithm that searched for significantly elevated velocity (30°/s). Saccade initiation and termination were defined as the beginning and end of the monotonic change in eye position during the high-velocity gaze shift.

The countermanding task provided the data for this study. All trials began when the monkey shifted gaze to fixate a centrally located stimulus for a variable interval (500-800 ms; Figure 3.1). Following this fixation interval, the central stimulus was removed and simultaneously a peripheral target was presented at one of two locations in opposite hemifields cuing the monkey to make a single saccade to the target. Targets were located along the horizontal axis and (10°) from the fixation target in the vast majority of sessions. For trials with no stop signal, monkeys were reinforced for making a saccade within 700 ms. In each behavioral session, the delay between fixation of the target and delivery of reinforcement was constant at 400 ms. On 20-50% of the trials, after a delay, referred to as the stop signal delay (SSD), the central fixation target reappeared, instructing the monkey to inhibit saccade initiation. Two outcomes were possible on these stop signal trials. Maintaining fixation on the stop signal for 700 ms after the target appeared was reinforced as correct; these trials were referred to as cancelled trials. On stop signal trials, a saccade to the target was considered incorrect, and thus resulted in a 1500 ms timeout with no reinforcecment. These trials were referred to as noncancelled trials. In each behavioral session, three to six SSDs of constant value ranging from 25 to 450 ms were used. The values were

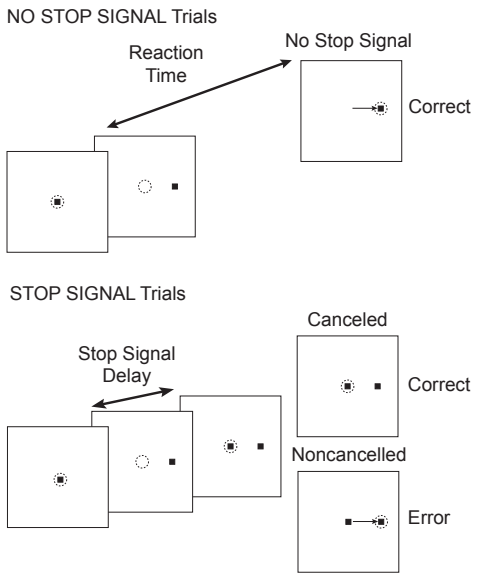

Figure 3.1: Trial displays for saccade countermanding task. Dotted circle indicates focus of gaze at each interval; arrow, the saccade. All trials began with presentation of a central fixation spot. After fixation of this spot for a variable interval, it disappeared simultaneous with presentation of a target on the left or right. In *no-stop signal trials*, a single saccade to the peripheral target was reinforced as the correct response. In *stop signal trials*, the fixation spot reappeared after a variable *stop signal delay*. Maintained fixation was reinforced as the correct response; these are referred to as *cancelled* (or signal-inhibit) trials. If a saccade was produced in spite of the stop signal, no reinforcement was given; these errors are referred to as *noncancelled* (or signal-respond) trials.

adjusted across sessions and monkeys to adjust for overall changes in response time so that, on average, monkeys failed to inhibit approximately half the stop signal trials.

Here we report data from 130 sites in the ACC of two monkeys. Data were recorded serially along acute single penetrations. An individual site consisted of all the behavioral and neurophysiological data recorded from a single location in the cortex. Some of the behavioral and neurophysiological data from these monkeys have appeared in other publications (Hanes et al., 1998; Ito et al., 2003; Stuphorn et al., 2000; Stuphorn and Schall, 2006; Brown et al., 2008).

3.3.1 Data acquisition

LFPs were recorded using single tungsten microelectrodes (impedance: 2-5 MΩ at 1 kHz), nonreferenced single ended. The electrode signals were amplified with a high-input impedance head stage (¿1 GΩ , ∼2 pF of parallel input capacitance) and filtered by a Multichannel Acquisition Processor (Plexon, Dallas, TX). The LFP data were filtered between 0.7 and 170 Hz with two cascaded one-pole low-cut Butterworth filters and a four-pole high-cut Butterworth filter and was sampled at 1 kHz. The reference used for both spikes and LFP was the same ground wire on the head-stage.

3.3.2 Data analysis

All recording sites were assessed for the occurrence of excessive noise. Recordings with recurring artifacts during time intervals of interest were excluded from analysis. The mean voltage in the 300 ms preceding target presentation for each valid trial was defined as the baseline and subtracted from the voltage for each trial. SSDs were varied according to the monkeys' performance so that at the shortest SSD, monkeys generally inhibited the movement in ¿75% of the stop signal trials and at the longest delay, monkeys inhibited the movement in ¡25% of the stop signal trials. No selection was made on the basis of whether or not the LFP displayed task-related activity.

To identify intervals of significant LFP modulation across different trial types, single trial LFPs were time synchronized to stimulus presentation or saccade initiation and then time averaged for each trial type. The event-related LFPs were then filtered using a 50th-order low-pass finite impulse response digital filter with a cutoff of 30

Hz. A difference wave was produced by subtracting the time-synchronized activity in one condition from the other (e.g., noncancelled – latency-matched no stop). For all comparisons between trial types, the onset of a significant difference was defined as the instant the difference wave exceeded ±2 SD for ≥50 ms and achieved a difference of ±3 SD during that interval. This criterion was used to compare the LFP on trials with no stop signal to the LFP on cancelled and noncancelled trials.

The rationale and approach for the race model analysis of the countermanding data have been described in detail previously (Hanes and Schall, 1995; Hanes et al., 1998; Logan et al., 1984). Briefly, the data obtained in the countermanding task are the inhibition function and the distribution of reaction times in no-stop signal trials. Inhibition functions plot the probability of noncancelled trials as a function of SSD and were fit with a cumulative Weibull function. The stop signal reaction time (SSRT), the length of time that was required to cancel the saccade, was estimated using two methods (reviewed by Band et al. 2003a; Logan 1994). The first assumes that SSRT is a random variable, whereas the second method assumes that SSRT is constant (reviewed by Band et al. 2003a). We obtained an overall estimate of SSRT estimates derived from both methods. An analysis of these data based on the race model was done to estimate the SSRT from the behavioral data collected while recording from each site in the ACC. Hanes et al. (1998) established the central benefit of the countermanding paradigm as capable of determining whether neural activity generates signals sufficient to control the production of movements. For some neural activity to play a direct role in controlling the initiation of an eye movement, it must be different during trials in which a saccade is initiated as compared with trials in

which the saccade is inhibited. Moreover, this difference in activity must occur by the time the movement was cancelled.

To determine if LFPs recorded from the ACC were modulated in a manner sufficient to control the production of saccades, we compared the LFP on cancelled trials to the LFP on no-stop signal trials with saccade latencies greater than the SSD plus the SSRT. According to the race model, these are the no-stop signal trials in which the GO process was slow enough that the STOP process would have finished before the GO process if the stop signal had occurred. The onset of significant differential activity was measured for each SSD collected at each site in the ACC. If significant modulation was measured, the time of that modulation was compared with the SSRT estimated from the behavioral data collected during each recording. To determine if LFP modulation was proportional to response conflict, the average polarity difference between cancelled and latency-matched no-stop signal trials was measured following the analysis of Stuphorn et al. (2000). To determine if the LFP signaled error or feedback, we measured polarization following saccade initiation and reward delivery. For each site, the LFP synchronized on saccade initiation on noncancelled trials was compared with the LFP synchronized on saccade initiation on no-stop signal trials. Response-synchronized LFPs were produced for saccades to each target separately and collapsed across targets.

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3.4 Results

3.4.1 Event-related LFP in ACC

In macaque monkeys performing the saccade stop signal task, the LFP recorded from the dorsal bank of the ACC exhibited weak stimulus-related and presaccadic negative polarization and pronounced postsaccadic modulation (Figure 3.2). Note that in this and all subsequent figures plotting voltage on the ordinate, negative is up. Stimulus-evoked modulation of the intracranial LFP was common but of low magnitude. Stimulus-evoked LFP modulation was equally common for targets presented

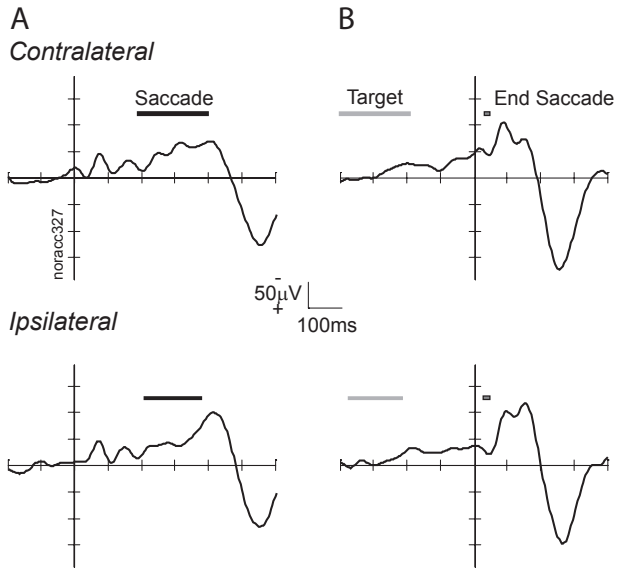

Figure 3.2: Event-related local field potentials (LFP) in anterior cingulate cortex (ACC) from representative site. A: LFP from no-stop signal trials synchronized on target presentation for contralateral (top, 149 trials) and ipsilateral (bottom, 143 trials) target. □, range of saccade latencies. B: LFP synchronized on initiation of saccade to contralateral (top) and ipsilateral (bottom) target. □, range of target onset times.

contralateral (77/130) or ipsilateral (70/130) to the recording site. The mean latency of the LFP modulation evoked by contralateral targets was 188 ± 101 (SD) ms and that for ipsilateral targets was 201 ± 77 ms. The onset latency was not different for ipsiversive versus contraversive saccades ($P = 0.30$; $\chi^2 = 1.06$, Kruskal-Wallis rank sum test).

The LFP at a minority of sites in the ACC tended to become more negative immediately preceding saccade initiation, corresponding to a readiness potential (Evdokimidis et al., 1992; Everling et al., 1996b). This was observed at 19% (25/130 sites) for contraversive and 9% (12/130 sites) for ipsiversive saccades. The mean onset of this modulation relative to saccade initiation was 21 ± 14 ms for contraversive and 29 ± 16 ms for ipsiversive saccades.

Postsaccadic modulation of the LFP in the ACC was almost always observed and stronger than the presaccadic modulation. Overall we identified LFP modulations in the interval following the saccade in 91% (117/130) of the sites. LFP modulation was equally common following contraversive (106/130 sites) and ipsiversive (114/130 sites) saccades. This modulation began 47 $\pm$ 42 ms after contraversive and 69 $\pm$ 45 ms after ipsiversive saccades. The latency was significantly earlier after contraversive saccades (P ¡ 0.01; $\chi^2 = 30.73$, Kruskal-Wallis rank sum test).

3.4.2 Effects of stop signal on stimulus-evoked LFP

The logic of the stop signal task and the measurement of SSRT using the race model suggest particular comparisons between stop signal and no-stop signal trials. First, cancelled stop signal trials can be compared with those no-stop signal trials with latencies long enough that the saccade would have been cancelled if a stop signal had occurred. Specifically, the LFP from cancelled stop signal trials can be compared with the LFP from no-stop signal trials with saccade latencies greater than SSD + SSRT. Second, noncancelled stop signal trials can be compared with those no-stop signal trials with latencies short enough that the saccade would not have been cancelled if a stop signal had occurred. Specifically, the LFP from noncancelled stop signal trials can be compared with the LFP from no-stop signal trials with saccade latencies less than SSD + SSRT. We refer to the subset of no-stop signal trials compared with either cancelled or noncancelled stop signal trials as *latency-matched*.

Figure 3.3 illustrates these comparisons for stimulus-aligned LFPs from a representative site in the ACC. Consider first the comparison between cancelled trials and

latency-matched no-stop signal trials (Figure 3.3A). When examined in this manner, movement- and fixation-related but not visual neurons in the FEF and the SC exhibit a pronounced modulation in cancelled trials occurring before the SSRT (Hanes et al., 1998; Paré and Hanes, 2003). This modulation occurs in a manner and at a time sufficient to be interpreted as controlling whether the saccade is initiated.

We observed a significant difference between the LFP recorded on cancelled trials and that recorded on latency-matched no-stop signal trials in only 38% (206/537) of the SSDs sampled across 130 sites in the ACC. In approximately half of these SSDs (21%, 104/537), the LFP polarity on cancelled trials was more negative than on no-stop trials, and in the other half (20%, 102/537), the LFP on cancelled trials was more positive than on no-stop trials. However, this polarity difference occurred on average 220 ± 98 ms after the SSRT. A significant polarization difference between cancelled trials and no-stop trials before the SSRT occurred for only 2 of the 537 SSDs sampled. This result clearly demonstrates that presaccadic LFPs in the ACC do not modulate in a manner sufficient to control the initiation of saccades.

Consider next the comparison between noncancelled trials and latency-matched no-stop signal trials (Figure 3.3B). A critical assumption of the race model is that the GO and STOP processes are independent (Logan et al., 1984). Hanes et al. (1998) tested the assumption of independence (whether the presence of the STOP process affected the timing of the GO process) by comparing the target aligned neural activity on noncancelled trials to latency-matched no-stop signal trials. When examined in this manner, neurons in the FEF and the SC exhibit identical activation in noncancelled and no-stop signal trials (Hanes et al., 1998; Paré and Hanes,

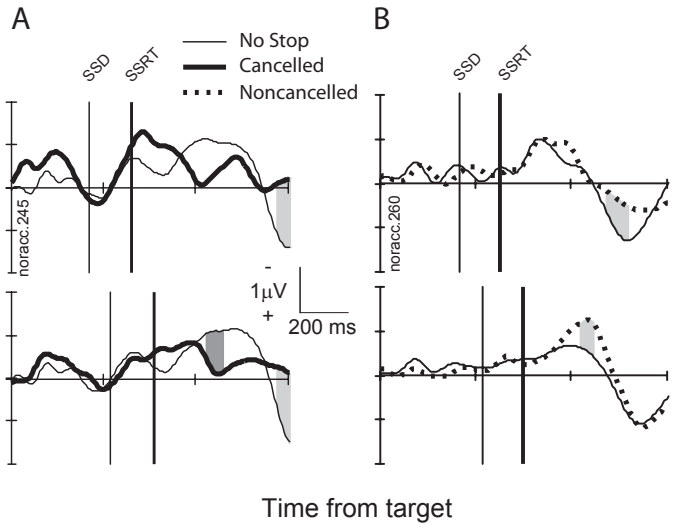

Figure 3.3: LFP in stop signal trials from a representative site. A: comparison of LFP in cancelled stop signal trials (thick) and latency-matched no-stop signal trials (thin) with stop signal delays of 169 ms (top, 198 no-stop trials trials; 26 cancelled trials) and 217 ms (bottom, 137 no-stop trials; 58 cancelled trials). Intervals in stop signal trials in which polarity is significantly more negative are highlighted by dark gray. Intervals in stop signal trials in which polarity is significantly more positive are highlighted by light gray. B: comparison of LFP in noncancelled stop signal trials (thick, dotted) and latency-matched no-stop signal trials (thin) with stop signal delays of 217 ms (top, 67 no-stop trials; 19 cancelled trials) and 269 ms (bottom, 165 no-stop trials; 49 cancelled trials).

2003). We compared the LFP polarization on noncancelled trials to that on no-stop signal trials with saccade latencies less than SSD + SSRT. These are the no-stop signal trials in which the GO process was fast enough that the GO process would have finished before the STOP process if the stop signal had been presented. On 37% (222/589) of the SSDs across 130 sites in the ACC, we observed a significant LFP modulation for noncancelled trials versus latency-matched no-stop signal trials with half (110/589) showing greater negativity and half (112/589) showing greater positivity in noncancelled trials. The overall latency of this modulation was 246 $\pm$ 139ms after the SSRT. Thus presentation of the foveal visual stop signal does not influence ACC LFP polarization on noncancelled trials before the SSRT.

3.4.3 Tests of ACC LFP conflict signal

Botvinick et al. (2001) postulated that conflict between incompatible response processes signals the need for control by the executive system. This hypothesis can be evaluated using behavioral performance and physiological data from the saccade stop signal task in two ways.

The first test involves relating LFP signals in the ACC to the amount of response conflict in different trials. Performance in countermanding tasks can be accounted for by a race between GO and STOP processes (Logan et al., 1984); in the saccade stop signal task this race is accomplished through the interaction between gaze-shifting and -holding circuits in the FEF and SC (Hanes et al., 1998; Paré and Hanes, 2003). In fact, an interactive race model with mutual inhibition between a GO unit and a STOP unit fits performance data as well as the independent race if and only if the

timing of modulation of the GO and STOP units correspond to the actual modulation times of movement and fixation neurons (Boucher et al., 2007b). In this framework, the coactivation of movement GO and fixation (STOP) units engenders response conflict. Now, cancelled trials include a period during which movement GO and fixation (STOP) neurons are coactive; this period of coactivation does not occur in noncancelled error trials because the fixation neurons (and the STOP unit in the model) do not turn on before the movement neurons (and the GO unit in the model) reach the threshold of activation to trigger the movement. Furthermore, the magnitude of coactivation of movement GO and fixation (STOP) units in cancelled trials increases as the probability of a noncancelled saccade increases; this occurs because the activation of the movement GO units grow progressively closer to the threshold. Thus a given amount of activation of fixation (STOP) units sufficient to inhibit the growing activation of movement GO units multiplied by the magnitude of activation of movement GO units will result in higher response conflict. A population of neurons in the ACC of monkeys performing the saccade stop signal task was modulated after SSRT to a degree that was proportional to the probability of a noncancelled saccade and so may signal response conflict (Stuphorn et al., 2000). Thus the first test of the conflict-monitoring theory is to determine whether the LFP exhibits polarity differences in cancelled as compared with latency-matched no-stop signal trials that vary systematically with the probability of a noncancelled saccade.

Figure 3.4 plots the stimulus-evoked LFPs for cancelled stop signal trials and for latency-matched no-stop signal trials at a single site in the dorsal bank of the ACC for the three of four SSDs with sufficient trials (¿10) to provide a reliable value.

The average difference in LFP polarity between the trial types was measured in the interval starting 50 ms before to 150 ms after SSRT. This interval was chosen because it corresponds to the interval in which single-unit modulation related to response conflict was observed in the SEF (Stuphorn et al., 2000). For this site, the LFP polarity difference between cancelled and latency-matched no-stop signal trials became more positive with SSD and increasing probability of producing an errant noncancelled saccade (Figure 3.4C). To determine whether the variation in LFP polarity difference was related to SSD or to performance, we analyzed the regression of the LFP polarity difference between trial types as a function of SSD and of the probability of producing a noncancelled saccade. The polarity difference in the LFP between cancelled and no-stop signal trials did not vary with SSD (slope = 0.0005, t = 0.61, P = 0.29; Figure 3.4D, top), but it did vary significantly with the probability of producing a noncancelled saccade in a stop signal trial (slope = 0.36, t = 4.17, P ¡ 0.01; Figure 3.4D, bottom). However, the polarity difference between cancelled and latency-matched no-stop signal trials decreased with the probability of failing to cancel the saccade. This is opposite the pattern of modulation of SEF neurons signaling conflict (Stuphorn et al., 2000) and also incompatible with the variation of response conflict in this task, which increases on canceled trials as a function of the decreasing probability of canceling.

The second test involves determining whether LFP signals in the ACC relate to adjustments of performance; specifically, the magnitude of the response time adjustment on a given trial should increase with the magnitude of conflict on the previous trial (e.g., Kerns et al. 2004). Consistent with this, saccade latency increases sig-

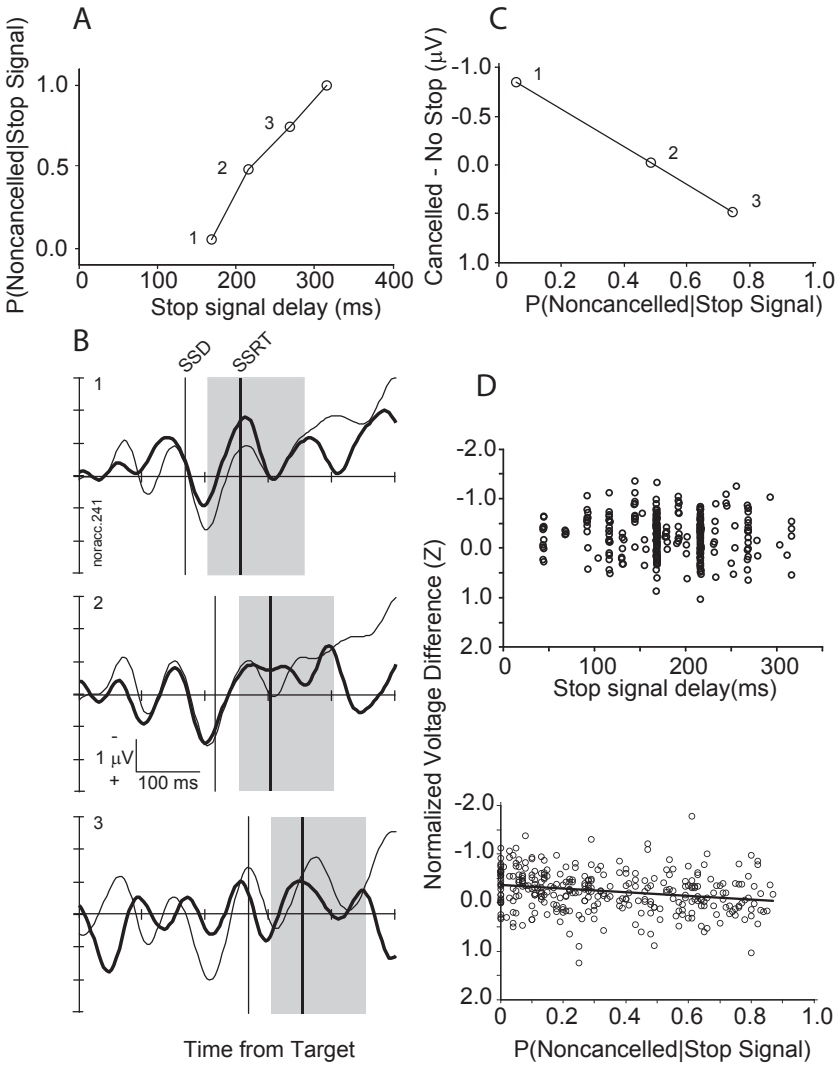

Figure 3.4: First test for conflict-related activity. A: inhibition function plots characteristic increasing probability of a noncancelled saccade as a function of stop signal delay. B: LFPs from representative site synchronized on stimulus onset for cancelled trials (thick solid line) at stop signal delays of 168, 216, and 268 ms (labeled in A) were compared with latency-matched no-stop signal trials (thin solid line). Average polarity difference between LFPs in cancelled and latency-matched no-stop signal trials in the interval from 50 ms before to 100 ms after stop signal reaction time (SSRT, highlighted by gray box) was measured. The vertical thin and thick black lines represent the stop signal delay (SSD) and SSRT, respectively. (B1: 215 no-stop trials, 51 cancelled trials; B2: 153 no-stop trials, 47 cancelled trials; B3: 55 no-stop trials, 15 cancelled trials). C: average polarity difference between cancelled and latency-matched no-stop signal trials plotted as a function of P (noncancelled—stop signal). The decreasing trend is significant. D: Z-scored average voltage difference across 314 stop signal delays plotted as function of SSD (top) and P (noncancelled—stop signal) (bottom). The polarity difference became significantly less negative with increasing P (noncancelled—stop signal).

nificantly following cancelled stop signal trials, which are the type of trial in which conflict between the GO and STOP units occurs (e.g., Emeric et al. 2007). We tested this prediction by measuring the trial-by-trial correlation between the LFP signal in the interval around SSRT in trial N and the response time adjustment in trial N + 1 (Figure 3.5). For each trial, the maximum negative-going deflection in the interval from 50 ms before to 150 ms after the SSRT was plotted against the adjustment in reaction time on the subsequent no-stop trial. Although a significant correlation was observed at some sites, across all the sites examined, response time adjustments were not correlated with the magnitude of the LFP negativity on cancelled trials. Thus according to another criterion, LFPs in the ACC do not appear to signal response conflict.

3.4.4 Tests of ACC LFP error signal

Modulation of the intracranial LFP following saccade production was common for both no-stop signal trials and noncancelled trials. Figure 3.6 plots comparisons of the response-synchronized LFPs from the ACC on noncancelled trials and all no-stop signal trials. The intracranial error-related potential was defined as the onset of the first significant negative-going potential following the saccade. Overall, an intracranial error-related potential was identified in 69% (89/130) of the sites when the LFP was combined across targets. This prevalence is evident by the clear polarization observed in the grand average LFP. In this grand average, a statistically significant negativity began 40 ms after the saccade; however, the largest quantitative negativity began ∼125 ms after the saccade. Measured across individual sites, this potential began

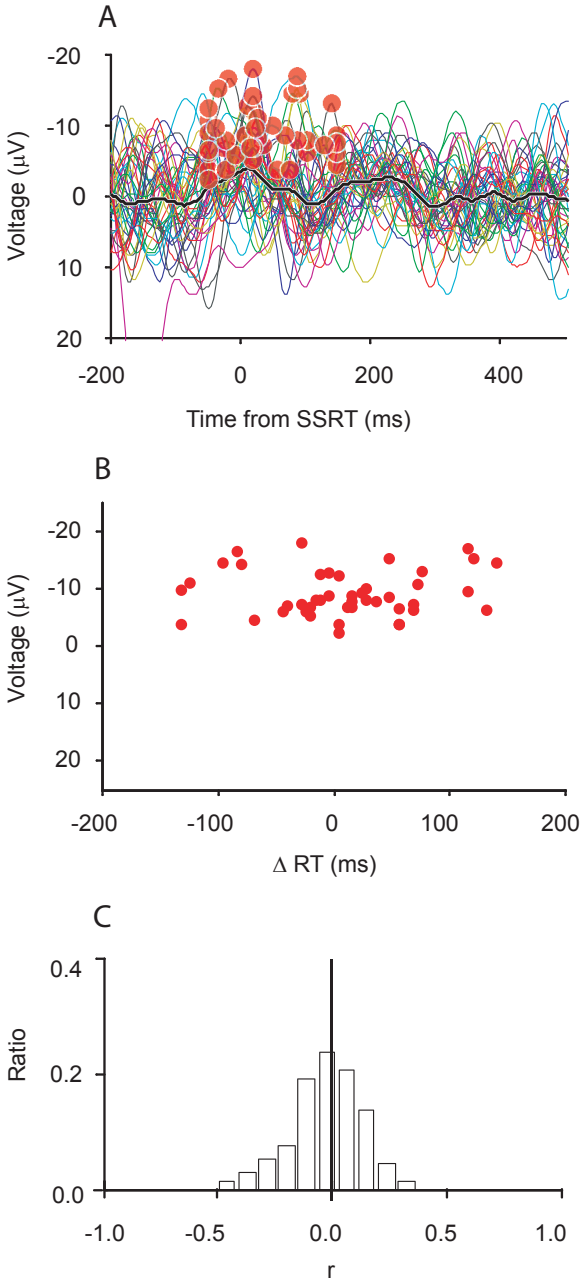

Figure 3.5: Second test for conflict related activity. A: LFP aligned on the estimate of SSRT for the subset of 45 cancelled stop signal trials that were followed by no-stop signal trials from a single session. Red circles mark peak negative polarity in the interval from 50 ms before to 150 ms after SSRT. B: peak negative polarity plotted as a function of the response time adjustment on the subsequent no-stop trial. No trend was evident. C: distribution of correlations between peak negativity in cancelled trials and response time adjustment in next trial. No relationship was found across all the sites examined.

148 ± 77 ms after saccade initiation. LFP modulation was equally common following contraversive (78/130 sites) or ipsiversive (74/130 sites) saccades. Measured site by site, the latency of this modulation following contraversive saccades was 181 ± 89 ms and that following ipsiversive saccades was 178 ± 57 ms; these distributions were not significantly different ($P = 0.31$; $\chi^2 = 1.04$, Kruskal-Wallis rank sum test). The earlier onset for the grand average and combined data as compared with the site-by-site values is a simple result of improving signal-to-noise through averaging.

We also observed a later, positive-going potential following errors. This was defined as the onset of the first significant positive-going potential following the saccade. Overall an intracranial error-related positive potential was identified in 82% (106/130) of the sites when the LFP was combined across targets. The error-related positivity in the grand average began 316 ms and peaked 424 ms after the onset of the error saccade. Measured across sites, this potential began 319 ± 84 ms after saccade initiation. The positivity was equally common following contraversive (84/130 sites) and ipsiversive (89/130 sites) saccades. Its latency following contraversive saccades (329 ± 64 ms) was not significantly different from that following ipsiversive saccades (334 ± 69 ms; $P = 0.41$; $\chi^2 = 0.67$, Kruskal-Wallis rank sum test).

We compared the latency of these negative- and positive-going error-related potentials to the onset of error-related spike rate modulation in the SEF and the ACC (Figure 3.7). Error-related unit modulation occurs earlier in the SEF than in the ACC (Ito et al., 2003). The negative-going potential in the ACC occurred later than the SEF error cell modulation (P ¡ 0.01; $\chi^2 = 16.66$, Kruskal-Wallis rank sum test) and synchronously with the ACC error cell modulation ($P = 0.55$; $\chi^2 = 0.36$, Kruskal-

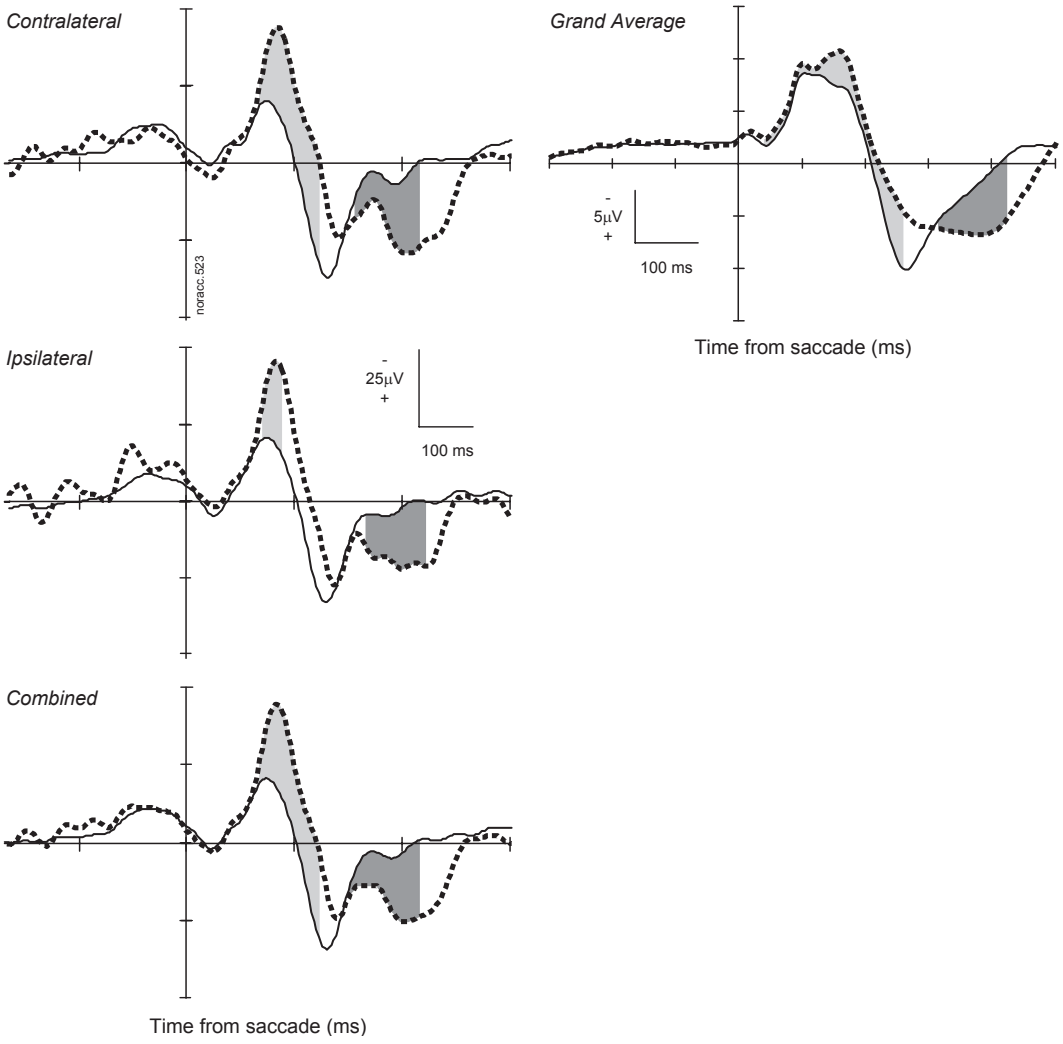

Figure 3.6: Error-related LFP. Left: LFP from a representative site aligned on saccade initiation for error noncancelled stop signal trials (thick dashed) and correct no-stop signal trials (solid) for contraversive (top, 172 no-stop trials; 17 cancelled trials), ipsiversive (middle, 168 no-stop trials; 11 cancelled trials), and both (bottom, 340 no-stop trials; 28 cancelled trials) saccades. Right: grand average LFP from 130 sites in the dorsal bank of the ACC aligned on saccade initiation for error noncancelled and correct no-stop signal trials. Intervals in which the polarity of noncancelled error LFP was significantly more negative than that in no-stop signal trials indicated by light gray fill. Intervals in which polarity of noncancelled error LFP was significantly more positive than that in no-stop signal trials indicated by dark gray fill.

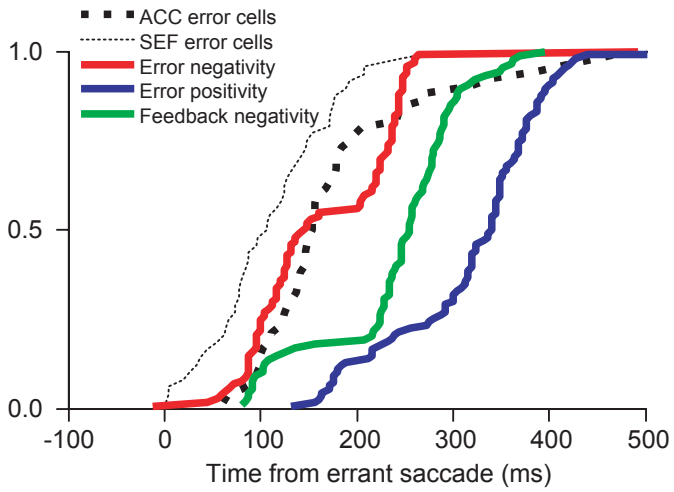

Figure 3.7: Cumulative distributions of onset of error-related negative polarity LFP (red), error-related positive polarity LFP (blue), and the feedback-related negative polarity LFP (green). These are compared with latency of error related units in supplementary eye field (SEF, thin black) and in ACC (thick black).

Wallis rank sum test). The positive-going error-related potential in the ACC occurred later than the SEF error cell modulation (P ¡ 0.01; $\chi^2 = 87.38$, Kruskal-Wallis rank sum test) and also later than the ACC error cell modulation (P ¡ 0.01; $\chi^2 = 55.91$, Kruskal-Wallis rank sum test).

Several studies have examined the relationship between the ERN and posterior adjustments (e.g., Debener et al. 2005Go). We examined the trial-by-trial covariation of the error-related LFP and the response time adjustment on the n + 1 trial (Figure 3.8). For each noncancelled trial, the maximum negative-going deflection in the 0 to 250 ms interval and the maximum positive-going deflection in the 200 to 500 ms interval after the errant saccade were plotted against the difference in reaction time on the subsequent no-stop trial. Although significant correlations were observed at some recording sites, response time adjustments were not correlated with the LFP peak negativity ($t = 0.88$, $P = 0.38$) or peak positivity ($t = 0.32$, $P = 0.75$) across

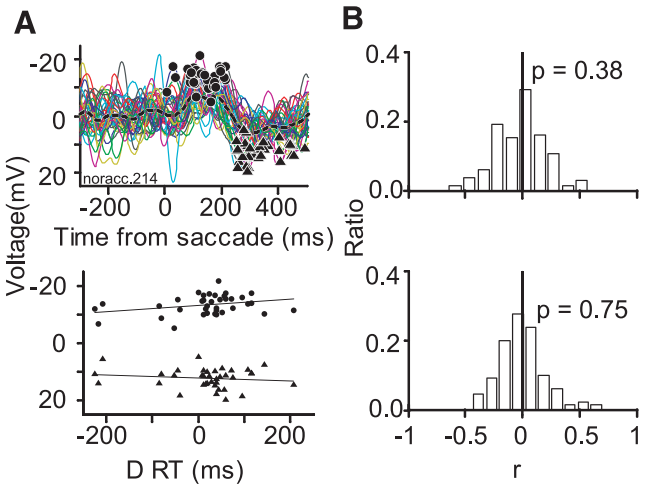

Figure 3.8: Error-related LFP and the response time adjustment. A: response-synchronized LFP for noncancelled stop signal trials that were followed by no stop signal trials (top). bullet, peak negative value in the 250-ms interval following the response on each of the 37 individual trials. blacktriangleup, peak positive value in 250- to 500-ms interval following the response on individual trials. Peak negative and positive polarization plotted against the response time adjustment on the subsequent no stop trial (bottom). B: correlation coefficients for peak negativity (top) and peak positivity (bottom) as a function of RT adjustment.

all the sites examined after errors had been produced (Figure 3.8B).

3.4.5 Tests of ACC LFP reinforcement-feedback signal

To determine whether LFPs in the ACC were modulated by feedback about reinforcement, we compared the LFPs synchronized on the time of reinforcement when it was delivered and when it was withheld in correct no-stop signal trials (Figure 3.9). This could be done because the delay between the end of the saccade to the target and delivery of reinforcement was fixed at 400 ms and therefore entirely predictable. A significant negative-going potential was measured in 40% (46/116) of the sites with the LFP combined across contraversive and ipsiversive saccades; this modulation began 256 $\pm$ 204 ms after the time when reinforcement would have been delivered. This

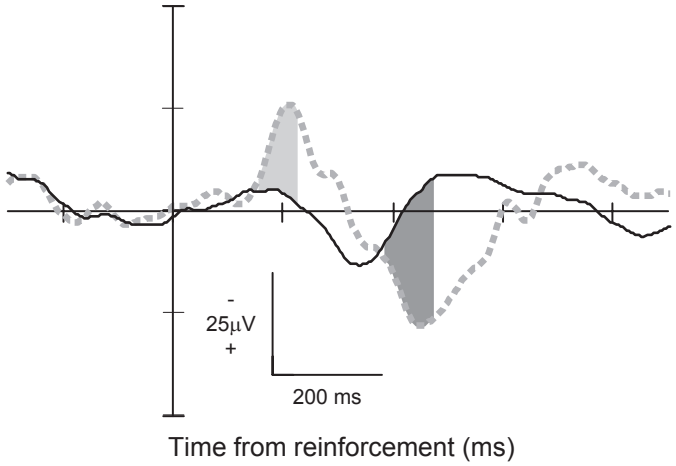

Figure 3.9: Feedback-related LFP from a representative site. LFP aligned on time of reinforcement following contra- and ipsiversive saccades in reinforced (solid) and unreinforced no-stop signal trials (461 rewarded no-stop trials; 35 unrewarded no-stop trials). The pattern of polarization resembles that observed following stop trial errors. Intervals on unreinforced trials in which the polarity was significantly more negative than that on reinforced trials is indicated by light gray fill; intervals of significantly more positive polarity indicated by dark gray fill. The significantly more negative polarity began 156 ms following time that reinforcement would have been delivered. The significantly more positive polarity began 388 ms after scheduled reinforcement.

latency was significantly longer than the error-related modulation after saccades (P ¡ 0.01; $\chi^2 = 40.64$, Kruskal-Wallis rank sum test). Thus LFPs in macaque ACC also signal reinforcement feedback.

3.4.6 Location of intracranial potentials

Nearly all of the intracranial error-related potentials were recorded from the dorsal bank of the anterior cingulate sulcus within area 24c as judged by depth relative to the overlying SEF and other landmarks. The sites with intracranial error-related potentials were distributed in a strip extending from 3 mm caudal to 4 mm rostral of the SEF (Figure 3.10). This region is coextensive with an area of the ACC that is

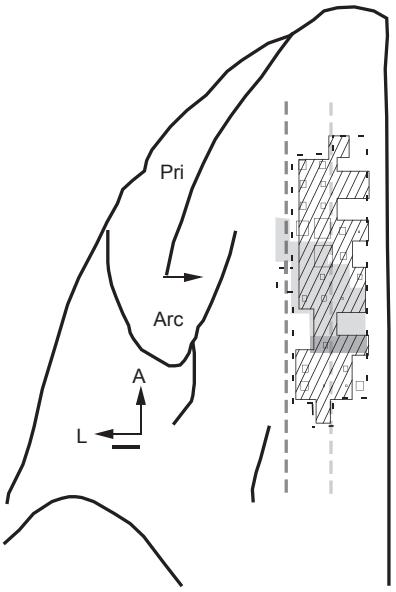

Figure 3.10: Location of sites with error LFP signals. Top view of the left frontal lobe of monkey N. Neural activity was sampled within the region bounded by the thin dashed line. The area in which error-related and reinforcement-related single-unit activity was encountered in ACC indicated by cross-hatching (from Ito et al. 2003Go). Number of error-related LFPs recorded indicated by the size of the squares. Single-unit and LFP signals were concentrated in the dorsal bank of the cingulate sulcus. Other landmarks include the extent of the SEF defined by low thresholds (¡50 A) for eliciting saccades with intracortical electrical stimulation (light gray fill), the rostral extent of the forelimb representation in the supplementary motor area (dark gray fill), the lateral extent of the gray matter in the medial wall (light gray dashed line), and the fundus of the cingulate sulcus (dark gray dashed line). These lines appear straight because the mediolateral extent of the cingulate sulcus varies little in the frontal lobe of macaques. The arcuate (Arc) and principal (Pri) sulci are labeled. Horizontal arrow marks 27 mm anterior to the interaural line. Scale bar, 1 mm.

reciprocally connected with the SEF (Huerta and Kaas, 1990), in which single units signal errors and the receipt of reinforcement (Ito et al., 2003).

3.5 Discussion

We observed error-related and reinforcement-feedback potentials in the dorsal bank of the ACC in macaque monkeys performing a saccade stop signal task. How-

ever, the error-related potentials did not covary with response time adjustments. Moreover, vanishingly few sites exhibited LFP modulation sufficient to control the initiation of saccades. Finally, the LFPs recorded from the ACC yielded no evidence of a signal consistent with conflict monitoring.

These results constitute an initial step toward bridging human electrophysiology and monkey neurophysiology. Several reports have described ERPs from human subjects performing stop signal tasks (Bekker et al., 2005a; De Jong et al., 1990, 1995; Dimoska et al., 2006; Kok et al., 2004; Naito and Matsumura, 1994a; Naito et al., 1995; Pliszka et al., 2000; Ramautar et al., 2004, 2006b,a; Stahl and Gibbons, 2007; van Boxtel et al., 2001). Although these have employed variations in task demand, stop stimulus modality, and effector, some general conclusions seem plausible. Larger N2 and P3 components are observed in stop signal as compared with no-stop signal trials. Latency and some magnitude differences in components are observed when comparing canceled and noncancelled stop signal trials. An enhanced N2 on noncancelled trials may be identified with the ERN. However, the N2 observed on canceled trials is difficult to identify conclusively with a measure of conflict. Also clear modulation of ERP components before SSRT when movements are canceled in stop signal trials as compared with produced in no-stop signal trials has not been consistently reported. Source localization identifies the N2 and P3 components on canceled and noncancelled trials with different parts of the brain with the medial frontal cortex among other loci contributing. Although the results presented herein complement these observations, taken as a whole careful analysis of this body of work highlights the need for further investigation coordinated across species, task conditions, and

effectors.

3.5.1 Stimulus-related and postsaccadic modulation

LFPs in the ACC were much more polarized in the interval following saccade initiation than in the interval following stimulus onset. This is consistent with single-unit studies observing increased activity related to trial outcome following responses (Amiez et al., 2005, 2006; Isomura et al., 2003; Ito et al., 2003; Niki and Watanabe, 1979; Procyk and Joseph, 2001; Procyk et al., 2000; Shidara and Richmond, 2002). However, visual responses have been observed in the ACC that are contingent on the probability of reward (e.g., Koyama et al. 2001; Shidara and Richmond 2002; Shima et al. 1991 as well as in the context of the saccade stop signal task (Pouget et al., 2005). The ACC receives few visual afferents, mainly from area PO, area 7a in the inferior parietal lobule, and inferotemporal area TG (Van Hoesen et al., 1993), the SEF (Huerta and Kaas, 1990; Luppino et al., 1990) and a diffuse connection with FEF (Huerta et al., 1987; Stanton et al., 1993; Wang et al., 2004). This may account for the result that the LFP at fewer sites in the ACC were modulated in the interval following the stimulus as compared with the interval following the saccade.

3.5.2 Response control

Anatomical data have been interpreted as evidence for the ACC contributing to high level response control (e.g., Dum and Strick 1991; Morecraft et al. 1992; Morecraft and Hoesen 1993; Paus 2001. Apparent movement-related single-unit activity has been described in the ACC for self-paced and stimulus-triggered arm movements

(Shima et al., 1991). Skeletal and ocular movements can be evoked by electrical microstimulation of the ACC (Hughes and Mazurowski, 1962; Luppino et al., 1991; Mitz and Godschalk, 1989; Showers, 1959; Talairach et al., 1973). Thus ACC can be described as an ocular motor cortical area like FEF or SEF.

The countermanding paradigm provides a clear criterion for determining whether neural activity generates signals sufficient to control the production of movements. The key test is whether the activity of neurons if different between trials with a movement (no-stop signal or noncancelled trials) and trials with no movement (cancelled trials), and, critically, whether such a difference occurs before SSRT. If some neural modulation occurs after SSRT, then according to the race model that identifies SSRT with the time of inhibition of the movement the modulation is too late (Boucher et al., 2007b; Logan et al., 1984).

Prior studies showed that movement and fixation but not visual neurons in the frontal eye fields and superior colliculi provide signals sufficient to control gaze (Hanes et al., 1998; Paré and Hanes, 2003). Specifically, on both no-stop signal and noncancelled trials, the activity of movement neurons increases until the saccade is triggered, and the activity of fixation neurons decreases after the target is presented. In contrast, on cancelled trials, the activity of movement neurons approaches but does not achieve the level of activity at which the saccade is triggered, and the activity of fixation neurons, which had decreased after the target was presented, increases before the SSRT.

The present analysis of the ACC field potentials, revealed vanishingly few sites with LFP modulation when movements were canceled that was early enough to con-

tribute to controlling the initiation of the saccades. At sites with a significant LFP modulation on cancelled trials, the latency was much longer than the SSRT (Figure 3.3). This is consistent with the observation that saccades can be evoked by stimulation of few sites in the ACC (Luppino et al., 1991; Mitz and Godschalk, 1989; Talairach et al., 1973).

This evidence against the ACC having a direct role in the control of gaze shifts is generally consistent with the results of lesion studies in both humans and monkeys. Human ACC lesion patients are not deficient in producing simple saccades to visual stimuli but are deficient in the ability to voluntarily inhibit reflexive saccades (Paus et al., 1991) and in the production of antisaccades, memory guided saccades, and sequences of visually guided saccades (Gaymard et al., 1998). Macaques with ACC lesions have deficits specific to the maintenance and selection of responses associated with different rewards but not in basic task performance Kennerley2006,Rushworth2003.

3.5.3 Performance monitoring

A dipole for the ERN can be located in the ACC (e.g., Dehaene et al. 1994; Miltner et al. 1997; van Veen and Carter 2002). Both Falkenstein et al. (1991) and Gehring et al. (1993) initially proposed that the ERN/Ne reflects a comparison between the representations of the overt error response and the correct response. An ERN-like potential has also been identified in human intracerebral EEG recording (Brázdil et al., 2002a; Brázdil et al., 2005) and error-related field potentials in the medial frontal cortex of monkeys (Gemba et al., 1986) but not in monkeys performing a task that requires executive control. The ERN was originally interpreted as an error-detection

signal resulting from a mismatch between the response and the outcome of response selection (Falkenstein et al., 1990, 1991; Gehring et al., 1993). However, alternate accounts view the ERN as a brain signal reflecting detection of response conflict (Botvinick et al., 2001; Yeung et al., 2004) or representing the dopaminergic input to the ACC (Holroyd et al., 2002). Such hypotheses ultimately require measurements of single units and field potentials that can be compared with the surface field potentials. Finding an intracranial homologue of the ERN is a necessary bridge.

3.5.4 Response conflict

The absence of field potentials in the ACC signaling conflict during the saccade stop signal task is incompatible with the general conflict-monitoring hypothesis of ACC function. The modulation of the N2 event-related potential during high-conflict trials have been emphasized as evidence for this conflict hypothesis (Botvinick et al., 2001; Yeung et al., 2004). According to this interpretation, the N2 and the ERN originate from the same neural process but are just observed at different times; response conflict on correct trials is supposed to precede the response and is manifested as the N2, whereas response conflict on error trials follows the response and is manifested as the ERN. Central tenets of the conflict hypothesis are that conflict is produced when mutually incompatible responses are active and response times increase following trials with high conflict.

We tested both of these predictions. First, the magnitude of ACC field potential modulation did not increase with the probability of noncancelled saccades (Fig. 4). In fact, the magnitude of the modulation decreased as the probability of noncan-

celled saccades approached 1.0. This result is contrary to other studies that have observed ERPs that increase with the level of response conflict (Gehring and Fencsik, 2001; Yeung et al., 2004). Second, response time adjustment did not covary with the magnitude of ACC field potential modulation on the preceding cancelled trial (Figure 3.5).

Examinations of single-unit activity in the medial frontal cortex of monkeys performing the saccade stop signal task have reported distinct populations of neurons that are modulated for errors, reinforcement, and response conflict Ito et al. (2003); Stuphorn et al. (2000). Stuphorn et al. (2000) identified single units in the SEF modulated by response conflict on cancelled trials that were not modulated on non-cancelled trials as well as separate SEF neurons modulated by noncancelled errors and reinforcement. Ito et al. (2003) identified single units in the ACC modulated by errors and reinforcement but not response conflict. Field potentials, both those recorded from the scalp and intracranially, are hypothesized to be produced by standing synaptic dipoles, a signal to which action potentials may not contribute. Therefore further work is required to examine field potentials in the medial frontal cortex for components that may contribute to conflict-related potentials recorded from the scalp.

The possibility exists that species, task, and effector differences may contribute to the differences observed for countermanding saccades in macaque monkeys versus human manual responses in the context of a flanker or stroop task. However, the ERN is evoked by saccade errors in the stop signal and antisaccade tasks (Endrass et al., 2005; Nieuwenhuis et al., 2001), and functional imaging has revealed that the ACC is active for cancelled and noncancelled saccades (Curtis et al., 2005). Therefore

it is unlikely that the absence of ACC field potentials modulated by conflict is due to effector or task differences. Stahl and Gibbons (2007) have proposed an alternative account of conflict monitoring in the context of the manual version of the stop signal task. In their account, conflict is greater on noncancelled trials than on cancelled trials. Only one saccade can be produced at a time, but multiple simultaneous manual responses are common. Further investigation is required to determine if conflict produced for competing bimanual response representations differs from the conflict between competing gaze-shifting and -holding processes. This does not, however, rule out the possibility that conflict occurs in other parts of the medial frontal cortex. Conflict-related single-unit activity in the SEF and activation in the supplementary motor area have also been observed under conditions of response conflict (Garavan et al., 2003; Stuphorn et al., 2000).

Further evidence supporting this conclusion is found in the timing of the intracranial field potential relative to the human ERN. In humans performing manual stop signal tasks, an ERN is recorded that exhibits a peak negative deflection 80 ms after the error response (Kok et al., 2004; Ramautar et al., 2004, 2006b,a). Similarly, the ERN measured during an antisaccade task peaked ∼80 ms after error saccades (Nieuwenhuis et al., 2001). ERP components measured from the scalp are derived from LFPs distributed within some volume of tissue. We found that across individual sites, the ERN occurred as early as 12 ms before and as late as 300 ms after the errant saccade. Averaged across individual sessions, the intracranial error-related field potential began ∼150 ms after the errant saccade; however, in the grand average field potential, a significant negative-going polarization was measured beginning 40 ms and

peaking 104 ms after the saccade. Given known conduction time differences between larger human and smaller macaque brains, these time values are very comparable.

3.5.5 Error monitoring

Converging evidence from imaging, ERPs, and intracranial field potentials have implicated the ACC as the generator of the ERN (reviewed by Bush et al. 2000). In this investigation, we consistently observed negative-going potentials followed by positive-going potentials after noncancelled errors throughout the dorsal bank of the ACC in monkeys performing a saccade stop signal task. This LFP modulation was not observed when comparing correct cancelled stop signal trials to correct no-stop signal trials. Therefore the LFP modulation was not evoked by the stop signal. The LFP modulation occurred after both contra- and ipsiversive errant noncancelled saccades. Therefore it is unlikely that this modulation is due to a sensory or movement-evoked potential. We therefore interpret this LFP modulation as signaling the occurrence of an error. Intracranial error-related potentials have been previously observed in the ACC of macaque monkeys (Gemba et al., 1986). In addition, intracranial error-related potentials have been observed in humans that covary in time with potentials recorded at the scalp (Brázdil et al., 2002a; Brázdil et al., 2005). This evidence leads us to the conclusion that the error-related potentials observed in this study are intracranial analogs of the ERN/Ne and the Pe. Further work is required, though, to confirm that an ERN can be recorded extracranially in macaques.

Another line of evidence concerns the morphology of the polarization. Similar to the grand average error-related LFP reported here, the ERN waveform for saccades

appears double-peaked (Nieuwenhuis et al., 2001; Van 't Ent and Apkarian, 1999). However, the response-locked ERN may overlap with the stop signal-locked N2, therefore the negative-going potentials observed following noncancelled errors may reflect both stop signal and error-related processing (e.g., Dimoska et al. (2006); Ramautar et al. (2004, 2006b,a). Thus the topographic and temporal similarity between the human ERN and the intracranial error-related negative-going field potential in the macaque ACC suggests that the intracranial potential contributes to the dipole producing the surface potential.

The error-detection hypothesis originally included the premise that ERN magnitude relates to response time adjustments (Coles et al., 1995; Gehring et al., 1993). Several studies have examined this relationship with diverse results using ERPs (Debener et al., 2005; Gehring and Fencsik, 2001; Gehring et al., 1993; Scheffers et al., 1996) and fMRI (Debener et al., 2005; Garavan et al., 2003). We found that the variations in response time adjustment did not covary with the magnitude of error-related field potential modulation (negative- or positive-going) on the preceding noncancelled trial similar to other recent studies of human subjects (Gehring and Fencsik, 2001; Nieuwenhuis et al., 2001). However, the general interpretation of these results should acknowledge that response times do not increase systematically following noncancelled saccade errors (Cabel et al., 2000; Emeric et al., 2007), and the overwhelming majority of these saccades are not followed by an immediate corrective saccade back to the initial fixation (Ito et al., 2003). Thus it is possible that medial frontal error signals are not used to control response times in subjects performing the saccade stop signal task and are instead a generic monitor of the occurrence of errors

(e.g., Holroyd et al. 1998).

3.5.6 Reinforcement learning

The reinforcement learning hypothesis proposes that the frontocentral negativity is elicited by events signaling error, loss of reinforcement, or punishment (e.g., (Gehring and Willoughby, 2002b; Miltner et al., 1997). Holroyd et al. (2002) hypothesize that the mesencephalic dopamine system conveys a negative reinforcement learning signal to the frontal cortex when human participants commit errors in reaction time tasks. They also proposed that errors induce phasic changes in mesencephalic dopaminergic activity that is manifest through ACC activity producing the ERN. Consistent with this, single units in ACC that discharge after errors are also active when earned reinforcement is withheld (Ito et al. 2003; see also Niki and Watanabe 1979). Also in monkeys performing the saccade stop signal task, other neurons in ACC modulate in a manner directly paralleling dopamine neurons (Ito et al., 2003). In other words, single units in the ACC signal whether ongoing events are better or worse than expected.

Consistent with the single-unit data, we observed feedback-related modulation on correct no-stop signal trials when reinforcement was withheld. However, further examination is required to test whether these LFPs are modulated in a way consistent with the reinforcement learning hypothesis. In particular, if the reinforcement learning hypothesis were true, then the amplitude of the LFP in the ACC should be modulated by reinforcement predictability, being large for unexpected errors and absent or possibly of reversed polarity for unexpected rewards (e.g., Holroyd and Yeung 2003).

3.5.7 Source localization

The ERN has a frontocentral distribution over the scalp such that a dipole for the ERN can be located in the ACC (e.g., Dehaene et al. 1994; Miltner et al. 1997; van Veen and Carter 2002). However, being an inverse problem (Helmholtz, 1853), an effectively infinite number of dipoles can account for a given scalp potential topography. Intracranial recordings can contribute useful data to constrain the range of plausible solutions. We found prominent, mostly biphasic, LFPs resembling human scalp ERN/Pe potentials in the monkey ACC after noncancelled errors on stop signal trials. Our results are consistent with previous reports of error-related field potentials in the medial frontal lobe of macaques (Gemba et al., 1986). In addition, intracranial ERPs resembling scalp Ne/Pe potentials have been observed in ACC as well as several other cortical locations after incorrect trials in humans (Brázdil et al., 2002a; Brázdil et al., 2005).

These observations must be viewed with appropriate skepticism though. Due to superposition, potentials generated by local and remote sources and sinks add algebraically at any given point so interpreting field potentials entirely in terms of local generators is uncertain. Thus it is possible that the field potentials we observed in the dorsal bank of the ACC arose from dipoles in, for example, the ventral bank of the ACC or more dorsally in the SEF. Evidence against this concern, though, includes preliminary results we have obtained showing attenuated or absent error-related field potentials in the ventral bank of the ACC (**Emeric EE, Stuphorn V, Schall JD.** Error-related local field potentials in medial frontal lobe of macaques

during saccade countermanding. *Soc Neurosci Abstr* 79.20, 2003.) and significantly less common error-related negative polarization in the SEF (**Emeric EE, Leslie M, Pouget P, Schall JD.** Local field potentials in supplementary eye field of macaque monkeys during a saccade stop signal task: Performance monitoring. *Soc Neurosci Abstr* 398.9, 2007). Nevertheless, to resolve this localization problem most definitely, it will be necessary to record current source density across the medial frontal cortex, spanning the layers of the dorsal and ventral banks of the ACC (e.g., Dias et al. 2006).

3.5.8 Cingulate cortex and gaze control

We now consider how signals in the portion of the dorsal bank of the ACC, in which we found these LFP signals, might influence the ocular motor system. In doing so, though, it is critical to recognize that anatomical tracer studies have not been performed that restrict tracer injections to this portion of area 24c. Granting this, signals in the ACC can influence the ocular motor system because the rostral cingulate cortex of monkeys is oligosynaptically connected to extraocular motoneurons (Moschovakis et al., 2004). The ACC is only weakly connected with the FEF (Barbas1981b; Huerta1990,Stanton1993,VanHoesen1993,Vogt1987,Vogt1987a) and does not project to the SC (Fries, 1984).

Other routes for the ACC to influence saccade production are available. First, the region of the ACC in which we recorded performance monitoring LFP signals is reciprocally connected with the SEF (e.g., Huerta and Kaas 1990; Luppino et al. 2003). Previous work has shown that subthreshold microstimulation of the SEF improves performance of the stop signal task by monkeys by delaying saccade initi-

ation Stuphorn and Schall 2006. Second, the ACC might also influence performance through connections with prefrontal areas 9 and 46 (Barbas and Pandya, 1989; Selemon and Goldman-Rakic, 1988; Vogt et al., 1987), but the role of these areas in saccade countermanding has not been investigated so no more can be inferred at this time. Third, Aron et al. (2006) have emphasized a critical role of the subthalamic nucleus in response inhibition during a manual stop signal task. The subthalamic nucleus is innervated by the FEF and SEF but not ACC (e.g., Frankle et al. 2006; Huerta and Kaas 1990; Huerta et al. 1986). Finally, the ACC can exert a more subtle influence through its projections to the locus coeruleus (reviewed by Aston-Jones and Cohen 2005). Clearly, much more work is needed to determine the relative contributions of each of these pathways in the executive control of gaze.

3.5.9 Conclusion

This study provides evidence of an analog of the ERN in the ACC field potentials of monkeys performing a stop signal task. Electrophysiological studies have led to the current view that electrical potentials recorded at the scalp are the result of summed cortical LFPs, which are generated by the synchronous synaptic activity of populations of neurons. Finding error-related field potentials concomitantly with unit activity in the ACC provides a bridge between the human ERN literature and the monkey neurophysiology literature. These findings provide an avenue for more closely examining the neural events that give rise to human ERPs.

3.5.10 Grants

This work was supported by National Institutes of Health Grants F32-EY-017765, T32-MH-065782, R01-MH-55806, P30-EY-08126, and P30-HD-015052 and by Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience.

CHAPTER IV

PERFORMANCE MONITORING LOCAL FIELD POTENTIALS IN THE MEDIAL FRONTAL CORTEX OF PRIMATES: SUPPLEMENTARY EYE FIELD

4.1 Abstract

We describe intracranial local field potentials (LFP) recorded in the supplementary eye field (SEF) of macaque monkeys performing a saccade countermanding task. The most prominent feature at 90% of the sites was a negative-going polarization evoked by a contralateral visual target. At $\sim$ 50% of sites a negative-going polarization was observed preceding saccades, but in stop signal trials this polarization was not modulated in a manner sufficient to control saccade initiation. When saccades were canceled in stop signal trials, LFP modulation increased with the inferred magnitude of response conflict derived from the coactivation of gaze-shifting and gaze-holding neurons. At 30% of sites, a pronounced negative-going polarization occurred after errors. This negative polarity did not appear in unrewarded correct trials. Variations of response time with trial history were not related to any features of the LFP. The results provide new evidence that error-related and conflict-related but not feedback-related signals are conveyed by the LFP in the macaque SEF and are important for identifying the generator of the error-related negativity. [1]

[1]This chapter has been submitted for publication as Emeric EE, Leslie M, Pouget P, Schall JD. Performance monitoring local field potentials in the medial frontal cortex of primates: Supplementary eye field.

4.2 Introduction

Human errors in reaction time tasks are associated with the error-related negativity (referred to as ERN or Ne) and a later positive deflection (Pe) (e.g., Falkenstein et al. (1991); Gehring et al. (1993)). The ERN has a frontocentral distribution over the scalp and peaks $\tilde{1}00$ ms after the incorrect response in choice-reaction time tasks or the uninhibited response on no-go trials Scheffers et al. (1996). A dipole for the ERN can be centered in the anterior cingulate cortex (ACC) (e.g., Dehaene et al. (1994); Miltner et al. (1997); van Veen and Carter (2002)), but the confidence interval of the inverse solution includes more dorsal medial frontal cortex including the presupplementary and supplementary motor areas (e.g., Miltner et al. 1997).

A number of hypotheses have been proposed to explain the ERN/Ne and the function it performs. The initial account of the functional significance of the error-monitoring hypothesis proposes that the ERN/Ne reflects a comparison between the representations of the overt error response and the correct response (Falkenstein et al., 1991; Gehring et al., 1993). Two other hypotheses are based on computational models grounded in anatomical and physiological data. The response conflict hypothesis posits the medial frontal potential represents a specific occurrence of response conflict monitoring (Botvinick et al., 2001; Carter et al., 1998). The reinforcement learning theory (Holroyd et al., 2002) hypothesizes that the ERN/Ne is an evaluative function signifying worse than expected events. Previous work in this lab has described error- and feedback-related intracranial local field potentials (LFP) recorded in the anterior cingulate cortex (ACC) of macaque monkeys while countermanding saccades. These

monitoring signals were tested against these three prevailing hypotheses about the ERN that have been proposed to explain this signal and the function it performs (Reviewed by Taylor et al. (2007)).

The goal of this study was continue building the bridge between monkey single-unit data and human ERP and fMRI data by determining whether local field potentials (LFPs) signaling error, reinforcement, or conflict are observed in the SEF of macaque monkeys performing a saccade stop signal task. This task requires subjects to inhibit a response at various stages of preparation when a stop signal is presented (Hanes and Schall, 1995; Logan, 1994; Logan et al., 1984). A saccade version of the stop signal task has been used to examine the role of the frontal eye field and superior colliculus in controlling the initiation of saccades (Hanes et al., 1998; Paré and Hanes, 2003; Brown et al., 2008). In contrast to the frontal eye fields and the superior colliculus, the supplementary eye fields (SEF) and the ACC do not produce signals sufficient to control saccade initiation (Schall et al., 2002). Instead neurons in SEF signal error, reward, and conflict (Stuphorn et al., 2000), while neurons in ACC signal error, reward, and feedback (Ito et al., 2003) (see also Amiez et al. 2005, 2003; Matsumoto et al. 2007; Procyk et al. 2000; Nakamura et al. 2005).

The parallels between these human electrophysiology findings and the macaque neurophysiological findings suggest that they are different perspectives on a common functional system. However, this inference is weakened by the uncertainty introduced by differences between species (the last common ancestor of humans and macaques was 25 million years ago; Kumar and Hedges 1998) and measurements — mainly event-related potentials from the scalp and fMRI in humans and single-unit recordings

in macaques. Our laboratory has begun building an empirical bridge between these separate islands of observation by obtaining extracranial electrophysiological measures from macaque monkeys (Garr et al., 2008; Woodman et al., 2007) and intracranial field potential measures analyzed in the same manner as human event-related potentials (Emeric et al., 2008).

The goal of this study was to bridge between monkey single-unit data and human ERP and fMRI data by determining whether local field potentials (LFPs) signaling error, reinforcement, or conflict are observed in the SEF of macaque monkeys. The present study reports the characteristics of LFPs that were recorded simultaneously with single units in the SEF of monkeys performing the saccade stop signal task. We determined whether intracerebral negativities (like the ERN/Ne) and positivities (like the Pe) occur in the SEF when monkeys made countermanding errors. We also investigated whether the premovement LFPs were modulated in a manner sufficient to control saccade initiation. Finally, we determined whether LFPs in the ACC were modulated in a manner consistent with signaling response conflict. The results provide clear evidence that LFP in the SEF do not contribute to controlling saccade initiation and that error-, conflict-, and feedback-related LFP modulation occur in the SEF of macaque monkeys. These results provide unexpected, new insights into the cerebral source of the ERN.

4.3 Methods

Data were collected from 3 male bonnet monkeys (*Macaca radiata*: 8−10 kg. Designated F, M,and U) that were cared for in accordance with U. S. Department of

Agriculture and Public Health Service Policy on the humane care and use of laboratory animals. Each animal was tested for ∼4 h/day, 5 day/wk. During testing, water or fruit juice was given as positive reinforcement. Access to water in the home cage was controlled and monitored. Fluids were supplemented as needed. Detailed descriptions of all surgical procedures, electrophysiological techniques behavioral training, and tasks have appeared previously (Hanes and Schall, 1995; Hanes et al., 1998).

The experiments were under computer control to present stimuli, record eye movements, and deliver liquid reinforcement. Stimuli were presented on a video monitor (48 x 48°) using computer-controlled raster graphics (512 x 512 resolution or TEMPO Videosync 1280 x 1040 resolution). The fixation spot subtended 0.37° of visual angle, and the target stimuli subtended from 0.3 to 3° of visual angle, depending on their eccentricity and had a luminance of 10 or 30 cd/m^2 on a 1 cd/m^2 background. Eye position was monitored via a scleral search coil or a video-based infrared eye tracker (ASL, Bedford, MA) while monkeys were head-restrained and seated in an enclosed chair within a magnetic field. Saccades were detected using a computer algorithm that searched for significantly elevated velocity (30°/s). Saccade initiation and termination were defined as the beginning and end of the monotonic change in eye position during the high-velocity gaze shift.

The countermanding task provided the data for this study. All trials began when the monkey shifted gaze to fixate a centrally located stimulus for a variable interval (500−800 ms; Figure 4.1). Following this fixation interval, the central stimulus was removed and simultaneously a peripheral target was presented at one of two locations in opposite hemifields cuing the monkey to make a single saccade to the target. Tar-

gets were located along the horizontal axis and (10°) from the fixation target in the vast majority of sessions. For trials with no stop signal, monkeys were reinforced for making a saccade within 800 ms. In each behavioral session, the delay between fixation of the target and delivery of reinforcement was constant at 400ms. On 20−50% of the trials, after a delay, referred to as the stop signal delay (SSD), the central fixation target reappeared, instructing the monkey to inhibit saccade initiation. Two outcomes were possible on these stop signal trials. Maintaining fixation on the stop signal for up to 1500 ms after the target appeared was reinforced as correct; these trials were referred to as cancelled trials. On stop signal trials, a saccade to the target was considered incorrect, and thus resulted in a 1500 ms timeout with no reinforcecment. These trials were referred to as noncancelled trials. In each behavioral session, three to six SSDs of constant value ranging from 25 to 450 ms were used. The values were adjusted across sessions and monkeys to adjust for overall changes in response time so that, on average, monkeys failed to inhibit approximately half the stop signal trials.

Here we report data from 82 sites in the SEF of 3 monkeys. Neurophysiological data were recorded serially along acute single penetrations. An individual site consisted of all the behavioral and neurophysiological data recorded from a single location in the cortex.

4.3.1 Data acquisition

LFPs were recorded using single tungsten microelectrodes (impedance: 2−5 MΩ at 1 kHz), nonreferenced single ended. The electrode signals were amplified with a

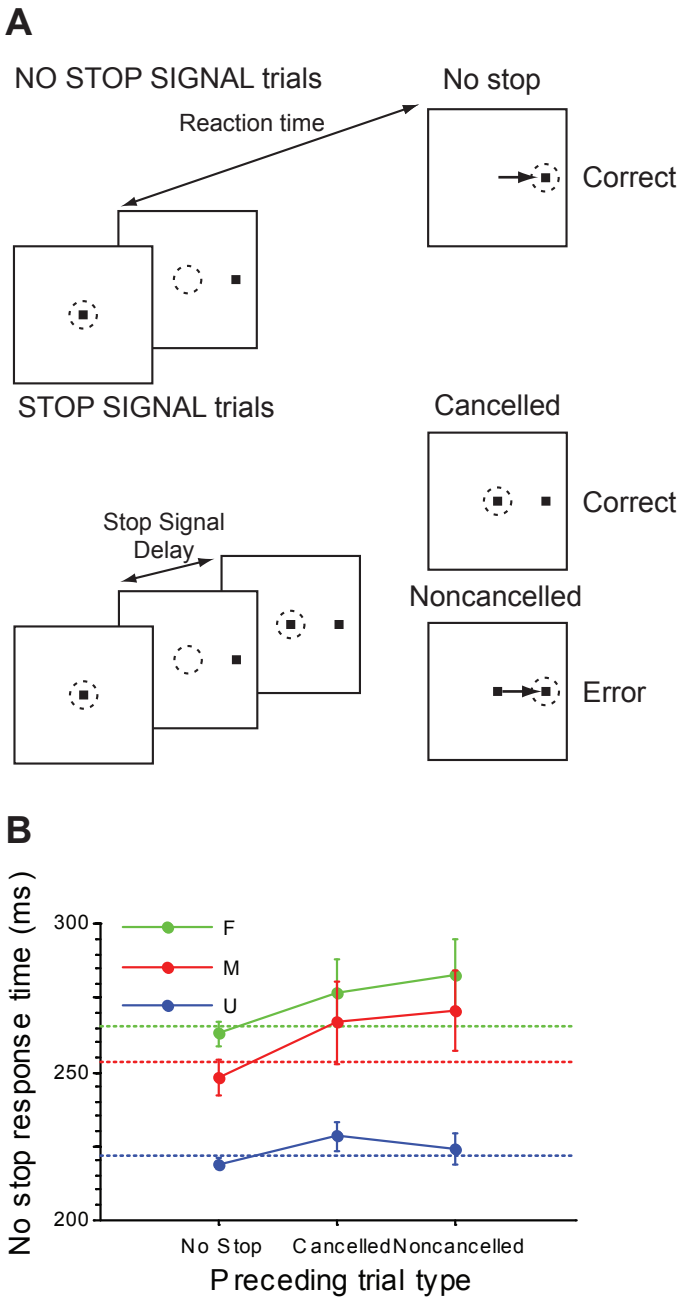

Figure 4.1: Trial displays for saccade countermanding task. Dotted circle indicates focus of gaze at each interval; arrow, the saccade. All trials began with presentation of a central fixation spot. After fixation of this spot for a variable interval, it disappeared simultaneous with presentation of a target on the left or right. In *no stop signal trials*, a single saccade to the peripheral target was reinforced as the correct response. In *stop signal trials*, the fixation spot reappeared after a variable *stop signal delay*. Maintained fixation was reinforced as the correct response; these are referred to as *cancelled* (or signal-inhibit) trials. If a saccade was produced in spite of the stop signal, no reinforcement was given; these errors are referred to as *noncancelled* (or signal-respond) trials.

high-input impedance head stage (> 1 GΩ , $\sim$2 pF of parallel input capacitance) and filtered by a Multichannel Acquisition Processor (Plexon, Dallas, TX). The LFP data were filtered between 0.7 and 170 Hz with two cascaded one-pole low-cut Butterworth filters and a four-pole high-cut Butterworth filter and sampled at 1 kHz. The reference used for both spikes and LFP was the same ground wire on the head-stage.

4.3.2 Data analysis

All recording sites were assessed for the occurrence of excessive noise. Recordings with recurring artifacts during time intervals of interest were excluded from analysis. The mean voltage in the 300 ms preceding target presentation for each valid trial was defined as the baseline and subtracted from the voltage for each trial. SSDs were varied according to the monkeys' performance so that at the shortest SSD, monkeys generally inhibited the movement in $> 75\%$ of the stop signal trials and at the longest delay, monkeys inhibited the movement in $< 25\%$ of the stop signal trials. No selection was made on the basis of whether or not the LFP displayed task-related polarization.

To identify intervals of significant LFP modulation across different trial types, single trial LFPs were time synchronized to stimulus presentation or saccade initiation and then time averaged for each trial type. The event-related LFPs were then filtered using a 50th-order low-pass finite impulse response digital filter with a cutoff of 30 Hz. A difference wave was produced by subtracting the time-synchronized LFP in one condition from that in the other (e.g., noncancelled-latency-matched no stop). For all comparisons between trial types, the onset of a significant difference was defined as the instant the difference wave exceeded ± 2 SD for $\geq$50 ms and achieved a difference

of ±3 SD during that interval. This criterion was used to compare the LFP on trials with no stop signal to the LFP on cancelled and noncancelled trials.

The rationale and approach for the race model analysis of the countermanding data have been described in detail previously (Hanes and Schall, 1995; Hanes et al., 1998; Logan et al., 1984). Briefly, the data obtained in the countermanding task are the inhibition function and the distribution of reaction times in no stop signal trials. Inhibition functions plot the probability of noncancelled trials as a function of SSD and were fit with a cumulative Weibull function. The stop signal reaction time (SSRT), the length of time that was required to cancel the saccade, was estimated using two methods (reviewed by Band et al. 2003a; Logan 1994). The first assumes that SSRT is a random variable, whereas the second method assumes that SSRT is constant (reviewed by Band et al. 2003a). We obtained an overall estimate of SSRT estimates derived from both methods. An analysis of these data based on the race model was done to estimate the SSRT from the behavioral data collected while recording from each site in the SEF. Hanes et al. (1998) established the central benefit of the countermanding paradigm as capable of determining whether neural activity generates signals sufficient to control the production of movements. For some neural activity to play a direct role in controlling the initiation of an eye movement, it must be different during trials in which a saccade is initiated as compared with trials in which the saccade is inhibited. Moreover, this difference in activity must occur by the time the movement was cancelled.

4.4 Results

4.4.1 Event-related LFP in SEF

In macaque monkeys performing the saccade stop signal task, the LFP recorded from SEF exhibited stimulus-related polarization, pronounced pre- and postsaccadic modulation, and auditory responses (Figure 4.2). Note that in this and all subsequent figures plotting voltage on the ordinate, negative is up according to convention. The stimulus evoked modulation of the LFP in SEF was an early negative deflection at times followed by a positive deflection within 100 ms of the stimulus onset (Figure 4.2A). Presaccadic negative-going modulation was also observed In order to minimize the contribution of any presaccadic LFP modulation to visually-evoked components only no stop signal trials with saccade latencies of greater than 200 ms were used to produce stimulus and saccade evoked potentials. The onset of a significant stimulus-evoked modulation was defined as the instant the stimulus synchronized wave exceeded ± 2 SD of the baseline for ≥ 25 ms and achieved a difference of ± 3 SD during that interval. Stimulus-evoked modulation of the intracranial LFP was observed at the majority of sites in the SEF. Significant stimulus-evoked LFP modulation was more common for targets presented contralateral (50/82 sites) than ipsilateral (35/82 sites) to the recording site. The mean $\pm$ standard deviation latency of the LFP modulation evoked by contralateral targets was 96 ± 57 ms and that for ipsilateral targets was 96 ± 48 ms. The onset latency was not different for ipsiversive versus contraversive targets ($P = 0.72$; $\chi^2 = 0.12$, Kruskal-Wallis rank sum test).

Presaccadic modulation was also observed (Figure 4.2B). To minimize the con-

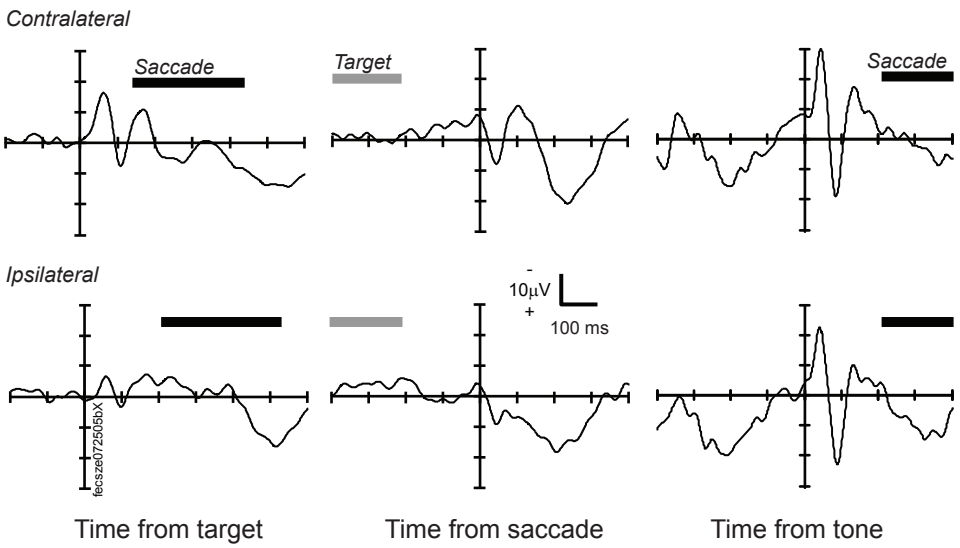

Figure 4.2: Event-related local field potentials (LFP) in the supplementary eye field (SEF) from representative site. A: LFP from no stop signal trials synchronized on target presentation for contralateral (top, 348 trials) and ipsilateral (bottom, 340 trials) target. B: LFP synchronized on initiation of saccade to contralateral (top) and ipsilateral (bottom) target. C: LFP synchronized on the auditory secondary reinforcer. □, the range of target onset, saccade onset, and the next saccade following reinforcement.

tribution of visually-evoked LFP modulation to presaccadic modulation only no stop signal trials with saccade latencies exceeding 200 ms were used to produce saccade evoked potentials. Presaccadic modulation was quantified by fitting a regression line to the saccade-evoked potential in the interval from 200 to 15 ms before the saccade. The evoked LFP was also examined with a Spearman correlation ($\alpha = 0.05$; Figure 4.2B). A significant correlation was observed at the majority of sites during this interval 87%(71/82) of the sites. The LFP became significantly more negative prior to contraversive saccades at 54% (44/82 sites) and more positive prior to ipsiversive saccades at (41/82) of the sites in SEF. Overall the LFP became more negative in the 185 ms prior to contraversive saccades (mean correlation across sites; r = -0.13) and

more positive prior to ipsiversive saccades (mean across sites; r = 0.05). Postsaccadic modulation of the LFP in the SEF was almost always observed. Overall we identified LFP modulations in the interval following the saccade in (71/82) of the sites. LFP modulation was equally common following contraversive (29/82 sites) and ipsiversive (25/82 sites) saccades. The modulation began 234 ± 125 ms after contraversive and 271 ± 120 ms after ipsiversive saccades. The latency was not significantly different for contraversive versus ipsiversive targets ($P = 0.30$; $\chi^2 = 1.08$, Kruskal-Wallis rank sum test).

A potential similar to visually-evoked potential was also observed following auditory stimuli (Figure 4.2C). Recall that 400 ms following a correct no stop signal saccade to the target, a secondary reinforcer in the form of a tone was presented at the same instant as the primary reinforcer and the target was extinguished. The monkeys would make a saccade away from the target shortly after reinforcement. Therefore, in order to minimize the contribution of the presaccadic modulation to these sensory components only no stop signal trials, saccade latencies — relative to the secondary reinforcer — of greater than 200 ms were used to produce stimulus-evoked and saccade-evoked potentials. For the potentials synchronized on the the secondary reinforcer, a biphasic potential was observed at a minority of sites (23/82) in the SEF both when the primary reinforcer was delivered or withheld starting at 85 ± 50 ms. This observation is consistent with SEF single unit auditory responses (Schall, 1991a; Tanji and Kurata, 1982; Wise and Tanji, 1981).

4.4.2 Effects of stop signal on stimulus-evoked LFP

The logic of the stop signal task and the measurement of SSRT using the race model suggest particular comparisons between stop signal and no stop signal trials. First, cancelled stop signal trials can be compared with those no stop signal trials with latencies long enough that the saccade would have been cancelled if a stop signal had occurred. Specifically, the LFP from cancelled stop signal trials can be compared with the LFP from no stop signal trials with saccade latencies greater than SSD + SSRT. Second, noncancelled stop signal trials can be compared with those no stop signal trials with latencies short enough that the saccade would not have been cancelled if a stop signal had occurred. Specifically, the LFP from noncancelled stop signal trials can be compared with the LFP from no stop signal trials with saccade latencies less than SSD + SSRT. We refer to the subset of no stop signal trials compared with either cancelled or noncancelled stop signal trials as latency-matched.

To determine if LFPs recorded from the SEF were modulated in a manner sufficient to control the production of saccades, we compared the LFP on cancelled trials to the LFP on no stop signal trials with saccade latencies greater than the SSD plus the SSRT. According to the race model, these are the no stop signal trials in which the GO process was slow enough that the STOP process would have finished before the GO process if the stop signal had occurred. The onset of significant differential activity was measured for each SSD collected at each site in the SEF. If significant modulation was measured, the time of that modulation was compared with the SSRT estimated from the behavioral data collected during each recording. To determine if

LFP modulation was proportional to response conflict, the average polarity difference between cancelled and latency-matched no stop signal trials was measured following the analysis of Stuphorn et al. (2000). To determine if the LFP signaled error or feedback, we measured polarization following saccade initiation and reward delivery. For each site, the LFP synchronized on saccade initiation on noncancelled trials was compared with the LFP synchronized on saccade initiation on no stop signal trials. Response-synchronized LFPs were produced for saccades to each target separately and collapsed across targets.

Figure 4.3 illustrates these comparisons for target-aligned LFPs from a representative site in the SEF. Consider first the comparison between cancelled trials and latency-matched no stop signal trials (Figure 4.3A). When examined in this manner, movement- and fixation-related but not visual neurons in the FEF and the SC exhibit a pronounced modulation in cancelled trials occurring before the SSRT (Hanes et al., 1998; Paré and Hanes, 2003; Brown et al., 2008). This modulation occurs in a manner and at a time sufficient to be interpreted as controlling whether the saccade is initiated.

We observed a significant difference between the LFP recorded on cancelled trials and that recorded on latency-matched no stop signal trials in only 5% (20/429 SSDs) of the SSDs sampled across 429 SSDs and 82 sites in the SEF. In approximately half of these few SSDs (2%, 8/429 SSDs), the LFP polarity on cancelled trials was more negative than on no stop trials, and in the other half (3%, 12/429 SSDs), the LFP on cancelled trials was more positive than on no stop trials. However, these polarity difference occurred on average 228 $\pm$ 205 ms (negative polarity difference) and 297

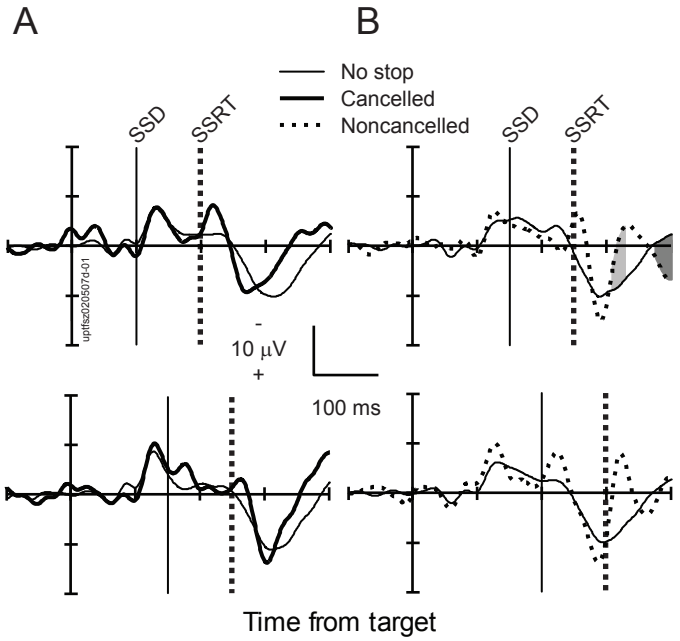

Figure 4.3: LFP in stop signal trials from a representative site. A: comparison of LFP in cancelled stop signal trials (thick) and latency-matched no stop signal trials (thin) with stop signal delays of 101 ms (top, 561 no stop trials trials; 49 cancelled trials) and 151 ms (bottom, 348 no stop trials; 59 cancelled trials). Intervals in stop signal trials in which polarity is significantly more negative are highlighted by dark gray. Intervals in stop signal trials in which polarity is significantly more positive are highlighted by light gray. B: comparison of LFP in noncancelled stop signal trials (thick, dotted) and latency-matched no stop signal trials (thin) with stop signal delays of 151 ms (top, 295 no stop trials; 45 noncancelled trials) and 201 ms (bottom, 478 no stop trials; 43 noncancelled trials

± 276 ms (positive polarity difference) after the SSRT. No significant polarization difference between cancelled trials and no stop trials occured before the SSRT. This result clearly demonstrates that presaccadic LFPs in the SEF do not modulate in a manner sufficient to control the initiation of saccades.

A critical assumption of the race model is that the GO and STOP processes are independent (Logan et al., 1984; Hanes et al., 1998) tested the assumption of independence (whether the presence of the STOP process affected the timing of the GO process) by comparing the target aligned neural activity on noncancelled trials to latency-matched no stop signal trials. When examined in this manner, neurons in the FEF and the SC exhibit identical activation in noncancelled and no stop signal trials (Hanes et al., 1998; Paré and Hanes, 2003). We compared the LFP polarization on noncancelled trials to that on no stop signal trials with saccade latencies less than SSD + SSRT (Figure 4.4A). These are the no stop signal trials in which the GO process was fast enough that the GO process would have finished before the STOP process if the stop signal had been presented. On 41% (174/429 SSDs) of the SSDs across 82 sites in the SEF, we observed a significant LFP modulation for noncancelled trials versus latency-matched no stop signal trials with 5% (25/429 SSDs) showing greater negativity, 10% (45/429 SSDs) showing greater positivity, and 24% (104/429 SSDs) showing a negative followed by a positive polarization in noncancelled trials. The overall latency of the negative modulation was 129 ± 166 ms after the SSRT. The overall latency of the positive modulation was 190 ± 144 ms after the SSRT. Thus presentation of the foveal visual stop signal did not influence SEF LFP polarization on noncancelled trials before the SSRT.

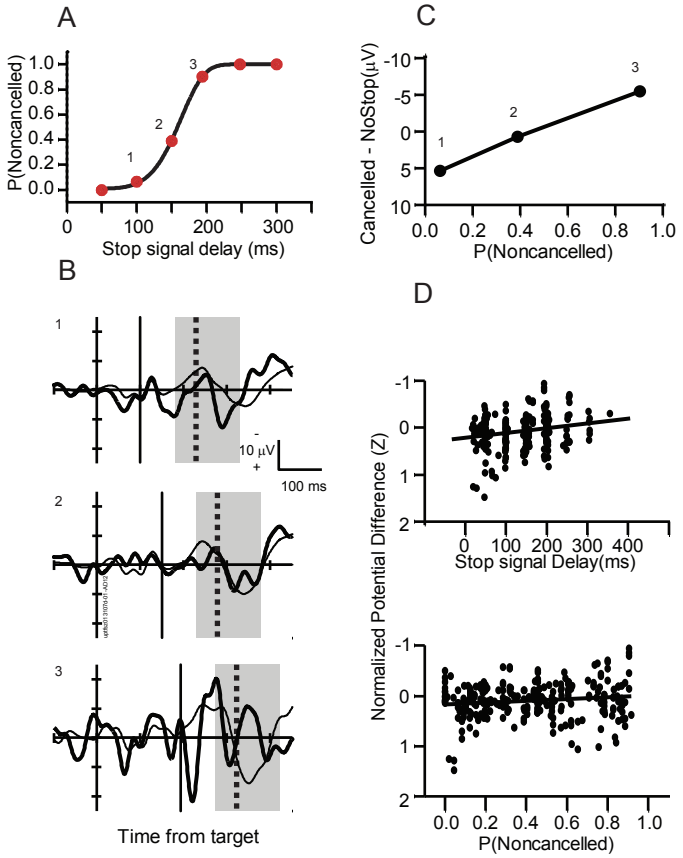

Figure 4.4: First test for conflict-related activity. A: inhibition function plots characteristic increasing probability of a noncancelled saccade as a function of stop signal delay. B: LFPs from representative site synchronized on stimulus onset for cancelled trials (thick solid line) at stop signal delays of 168, 216, and 268 ms (labeled in A) were compared with latency-matched no stop signal trials (thin solid line). Average polarity difference between LFPs in cancelled and latency-matched no stop signal trials in the interval from 50 ms before to 100 ms after stop signal reaction time (SSRT, highlighted by gray box) was measured. The vertical thin and thick black lines represent the stop signal delay (SSD) and SSRT, respectively. (B1: 42 no stop trials, 43 cancelled trials; B2: 289 no stop trials, 66 cancelled trials; B3: 72 no stop trials, 7 cancelled trials). C: average polarity difference between cancelled and latency-matched signal trials plotted as a function of P (noncancelled—stop signal). The increasing trend is significant. D: Z-scored average voltage difference across 436 stop signal delays plotted as function of SSD (top) and P (noncancelled—stop signal)(bottom). The polarity difference became significantly more negative with increasing stop signal delay and P (noncancelled—stop signal).

4.4.3 Tests of SEF LFP conflict signal

Botvinick et al. (2001) postulated that conflict between incompatible response processes signals the need for control by the executive system. This hypothesis can be evaluated using behavioral performance and physiological data from the saccade stop signal task in two ways. The first test involves relating LFP signals in the SEF to the amount of response conflict in different trials. Performance in countermanding tasks can be accounted for by a race between GO and STOP processes (Logan et al., 1984). In the saccade stop signal task this race is accomplished through the interaction between gaze-shifting and gaze-holding circuits in the FEF and SC (Hanes et al., 1998; Paré and Hanes, 2003). In fact, an interactive race model with mutual inhibition between a GO unit and a STOP unit fits performance data as well as the independent race if and only if the timing of modulation of the GO and STOP units correspond to the actual modulation times of movement and fixation neurons (Boucher et al., 2007b). In this framework, the coactivation of movement (GO) and fixation (STOP) units engenders response conflict. Now, cancelled trials include a period during which movement (GO) and fixation (STOP) neurons are unusually coactive; this period of coactivation does not occur in noncancelled error trials because the fixation neurons (and the STOP unit in the model) do not turn on before the movement neurons (and the GO unit in the model) reach the threshold of activation to trigger the movement. Furthermore, the magnitude of coactivation of movement (GO) and fixation (STOP) units in cancelled trials increases as the probability of a noncancelled saccade increases; this occurs because the activation of the movement

(GO) units grow progressively closer to the threshold. Thus a given amount of activation of fixation (STOP) units sufficient to inhibit the growing activation of movement (GO) units multiplied by the magnitude of activation of movement (GO) units will result in higher response conflict. A population of neurons in the SEF of monkeys performing the saccade stop signal task was modulated after SSRT to a degree that was proportional to the probability of a noncancelled saccade and so may signal response conflict (Stuphorn et al., 2000). Thus the first test of the conflict-monitoring theory is to determine whether the LFP exhibits polarity differences in cancelled as compared with latency-matched no stop signal trials that vary systematically with the probability of a noncancelled saccade.

Figure 4.4 plots the stimulus-evoked LFPs for cancelled stop signal trials and for the corresponding latency-matched no stop signal trials at a single site in the dorsal bank of the SEF for the three of six SSDs with sufficient trials (¿10) to provide a reliable value. The average difference in LFP polarity between the trial types was measured in the 200 ms interval starting 50 ms before the SSRT. This interval was chosen because it corresponds to the interval in which single-unit modulation related to response conflict was observed in the SEF (Stuphorn et al., 2000). For this site, the LFP polarity difference between cancelled and latency-matched no stop signal trials increased with SSD and increasing probability of producing an errant noncancelled saccade (Figure 4.4). To determine whether the variation in LFP polarity difference was related to SSD or to performance, we calculated the regression of the LFP polarity difference between trial types as a function of SSD and of the probability of producing a noncancelled saccade in a given session. The polarity difference in the LFP between

cancelled and no stop signal trials did vary with SSD (slope = -0.0013, r = -0.24, P ¡ 0.01; Figure 4.4D, top), as well as varying significantly with the probability of producing a noncancelled saccade in a stop signal trial (slope = -0.13, r = -0.13, P ¡ 0.01; Figure 4.4D, bottom). In addition, the polarity difference between cancelled and latency-matched no stop signal trials increased with the probability of failing to cancel the saccade.

The second test involves determining whether LFP signals in the SEF relate to adjustments of performance; specifically, the magnitude of the response time adjustment on a given trial should increase with the magnitude of conflict on the previous trial (e.g., Kerns et al. 2004). Consistent with this, saccade latency increases significantly following cancelled stop signal trials, which are the type of trial in which conflict between the GO and STOP units occurs (e.g., Emeric et al. 2007; see also Nelson et al. 2008). We tested this prediction by measuring the trial-by-trial correlation between the LFP signal in the interval around SSRT in trial N and the response time adjustment in trial N + 1 (Figure 4.5). For each trial, the maximum negative-going deflection in the 200 ms interval starting 50 ms the SSRT was plotted against the adjustment in reaction time on the subsequent no stop trial. Although a significant correlation was observed at some sites, across all the sites examined, response time adjustments were not correlated with the magnitude of the LFP negativity on cancelled trials. Thus according to this criterion, LFPs in the SEF do not appear to signal response conflict.

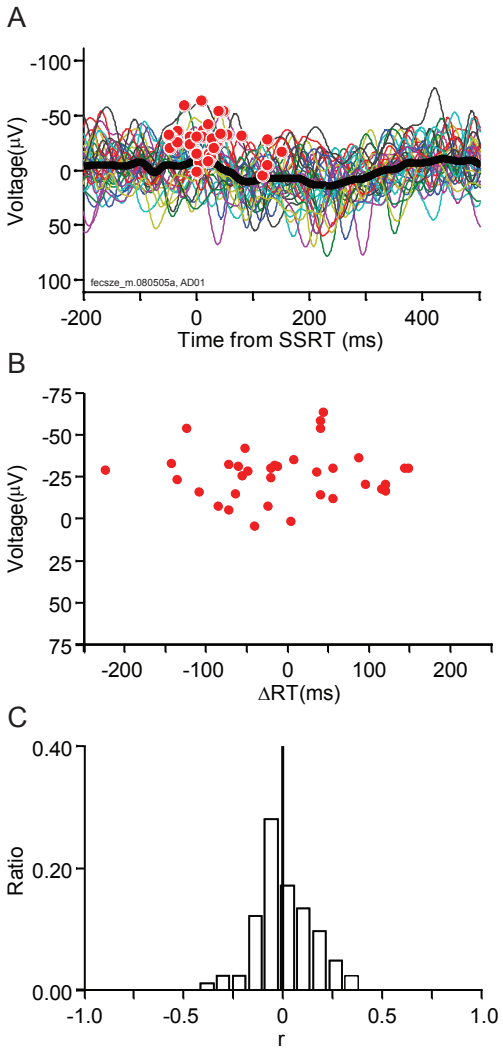

Figure 4.5: Second test for conflict related activity. A: LFP aligned on the estimate of SSRT for the subset of 35 cancelled stop signal trials that were followed by no stop signal trials from a single session. Red circles mark peak negative polarity in the interval from 50 ms before to 150 ms after SSRT. B: peak negative polarity plotted as a function of the response time adjustment on the subsequent no stop trial. No trend was evident. C: distribution of correlations between peak negativity in cancelled trials and response time adjustment in next trial. No relationship was found across the 82 sites examined.

4.4.4 Tests of SEF LFP error signal

Modulation of the intracranial SEF LFP following saccade production was common for both no stop signal trials and noncancelled trials. Figure 4.6 plots comparisons of the response-synchronized LFPs from the ACC on noncancelled trials and all no stop signal trials. The intracranial error-related potential was defined as the onset of the first significant negative-going potential following the saccade. Overall, an intracranial error-related potential was identified in 54% (44/82) of the sites when the LFP was combined across targets. We calculated a grand average LFP from the response-synchronized potential recorded across all 82 sites. The clear polarization observed at the individual sites is evident in the grand average LFP. In this grand average, a statistically significant negativity began 33 ms after the saccade and peaks 110 ms after the saccade. Measured across individual sites, this potential began 93 $\pm$ 44 ms after saccade initiation. LFP modulation was less common following contraversive (23/82 sites) than ipsiversive (35/82 sites) saccades. Measured site by site, the latency of this modulation following contraversive saccades was 105 $\pm$ 47 ms and that following ipsiversive saccades was 123 $\pm$ 58 ms; these distributions were not significantly different ($P = 0.53$; $\chi^2 = 0.53$, Kruskal-Wallis rank sum test).

We also observed a later, positive-going potential following errors. This was defined as the onset of the first significant positive-going potential following the saccade. Overall an intracranial error-related positive potential was identified in 66% (54/82) of the sites when the LFP was combined across targets. The error-related positivity in the grand average began 233 ms and peaked 461 ms after the onset of the error

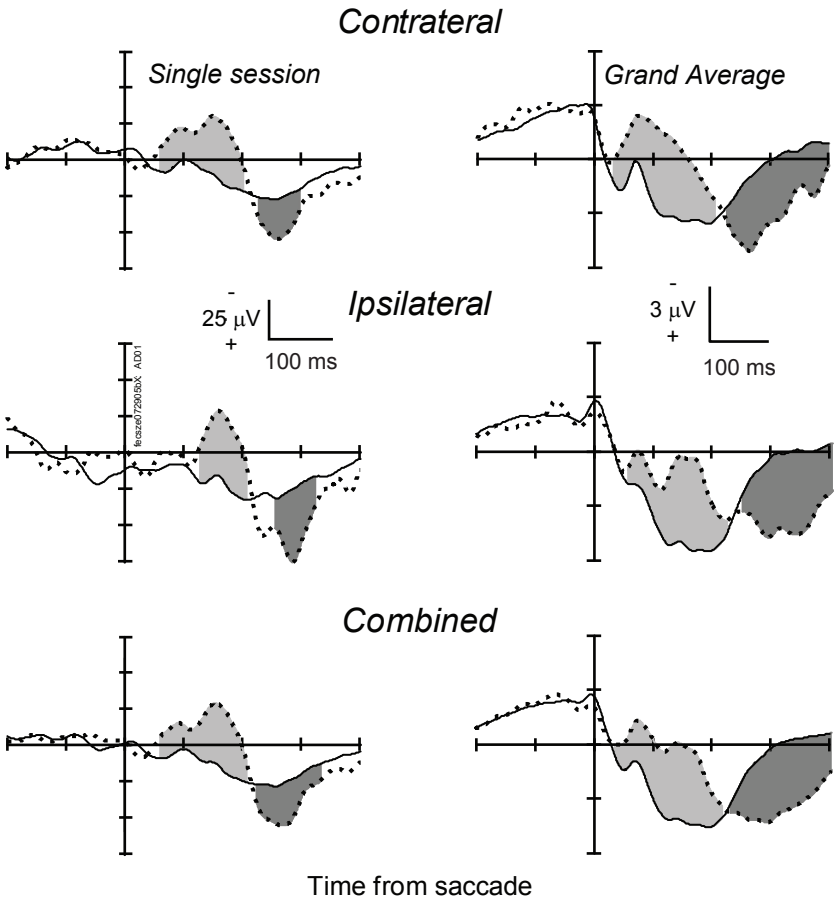

Figure 4.6: Error-related LFP. Left: LFP from a representative site aligned on saccade initiation for error noncancelled stop signal trials (thick dashed) and correct no stop signal trials (solid) for contraversive (top, 88 no stop trials; 34 noncancelled trials), ipsiversive (middle, 38 no stop trials; 13 noncancelled trials), and both (bottom, 126 no stop trials; 47 noncancelled trials) saccades. Right: grand average LFP from 82 sites in the SEF aligned on saccade initiation for contraversive(top), ipsiversive(middle), and combined (bottom)error noncancelled and correct no stop signal trials. Intervals in which the polarity of noncancelled error LFP was significantly more negative than that in no stop signal trials indicated by light gray fill. Intervals in which polarity of noncancelled error LFP was significantly more positive than that in no stop signal trials indicated by dark gray fill.

saccade. Measured across sites, this potential began 257 ± 89 ms after saccade initiation. The positivity was equally common following contraversive (36/82 sites) and ipsiversive (39/82 sites) saccades. Its latency following contraversive saccades (253 ± 102 ms) was not significantly different from that following ipsiversive saccades (271 ± 95 ms; $P = 0.13$; $\chi^2 = 2.25$, Kruskal-Wallis rank sum test).

We compared the latency of these negative- and positive-going error-related potentials to the onset of error-related spike rate modulation in the SEF (Stuphorn et al., 2000) and the ACC (Ito et al., 2003)(Figure 4.7). Error-related unit modulation occurs earlier in the SEF than in the ACC (Ito et al., 2003) and the negative-going error-related potential in ACC is coincident with the error-related unit modulation in ACC (Emeric et al., 2008). The negative-going potential in the SEF was coincident with the SEF error cell modulation ($P = 0.20$; $\chi^2 = 1.65$, Kruskal-Wallis rank sum test) and earlier than the ACC negative-going error potential (P ¡0.01; $\chi^2 = 28.37$, Kruskal-Wallis rank sum test). The positive-going error potential in the SEF occurred later than the SEF error cell modulation (P ¡ 0.01; $\chi^2 = 58.38$, Kruskal-Wallis rank sum test) and later than the ACC error cell modulation and the ACC negative-going error potential (P ¡ 0.01; $\chi^2 = 55.91$, Kruskal-Wallis rank sum test). The positive-going error-related potential in the SEF occurred earlier than the ACC positive-going error-related potential (P ¡ 0.01; $\chi^2 = 14.17$, Kruskal-Wallis rank sum test).

Several studies have examined the relationship between the ERN and post-error adjustments (e.g., Debener et al. 2005). We examined the trial-by-trial covariation of the error-related LFP and the response time adjustment on the n + 1 trial (Fig-

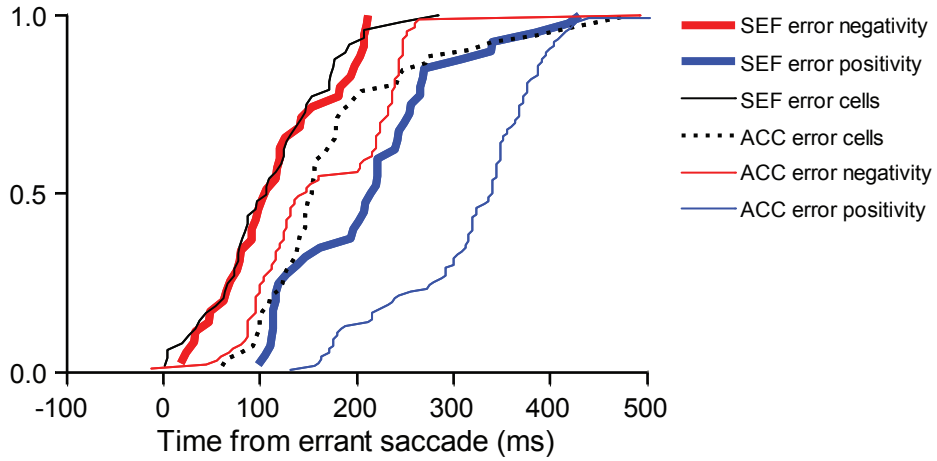

Figure 4.7: Cumulative distributions of onset of error-related negative polarity LFP (red), error-related positive polarity LFP (blue) in ACC and SEF. These are compared with latency of error related units in SEF (thin black) and in ACC (black dotted)

ure 4.8). For each noncancelled trial that was followed by a no stop signal trial, the maximum negative-going deflection in the 250 ms interval starting at the onset of the error saccade and the maximum positive-going deflection in the 300 ms interval starting 200 ms after the errant saccade were plotted against the difference in reaction time on the subsequent no stop trial. Significant correlations were observed at some recording sites and response time adjustments was correlated with the LFP peak negativity ($t = 2.45$, P ¡ 0.05) but not the peak positivity ($t = 0.34$, $P = 0.74$) across all the sites examined after errors had been produced (Figure 4.8B). However the sign of the correlation means that response times get longer as the negative-going deflection in SEF decreased in magnitude.

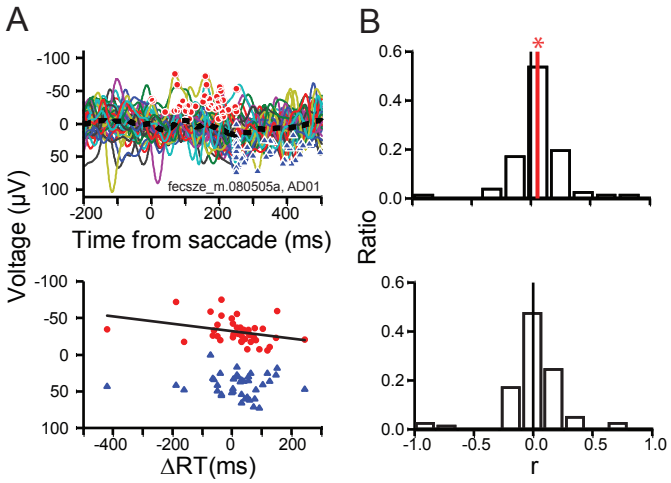

Figure 4.8: Error-related LFP and the response time adjustment. A: response-synchronized LFP for noncancelled stop signal trials that were followed by no stop signal trials (top). •, peak negative value in the 250-ms interval following the response on each of the 32 individual trials. △, peak positive value in 250- to 500-ms interval following the response on individual trials. Peak negative and positive polarization plotted against the response time adjustment on the subsequent no stop trial (bottom). B: correlation coefficients for peak negativity (top) and peak positivity (bottom) as a function of RT adjustment.

4.4.5 Tests of ACC LFP reinforcement-feedback signal

To determine whether LFPs in the SEF were modulated by feedback about reinforcement, neural signals can be synchronized on the time of reinforcement when it was delivered and when it was occasionally withheld in correct no stop signal trials. This could be done because the delay between the end of the saccade to the target and delivery of reinforcement was fixed at 400 ms and therefore entirely predictable. Emeric et al. (2008) observed a significant negative-going potential in the LFP recorded from ACC after the time when reinforcement would have been delivered compared to trials when reinforcement was delivered. Although we observed clear modulation relative to the tone (Figure 4.2C) we did not observe any significant potentials at any of the 82 sites examined. Thus the LFPs in macaque SEF do not

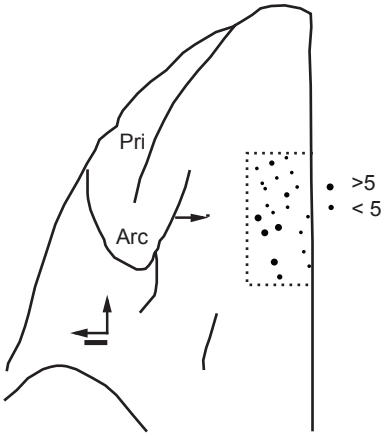

Figure 4.9: Location of sites with error LFP signals. Top view of the left frontal lobe of monkey U. Neural activity was sampled within the region bounded by the thin dashed line. Number of error-related LFPs recorded indicated by the size of the squares. The arcuate (Arc) and principal (Pri) sulci are labeled. Horizontal arrow marks 29 mm anterior to the interaural line. Scale bar, 1 mm.

signal reinforcement feedback.

4.4.6 Location of recording sites

Nearly all of the intracranial error-related potentials were recorded from the dorsal convexivity in area F7 of Matelli et al. (1991) as judged by the task-related activity of the encountered neurons in SEF, electrically evoked saccades, and anatomical landmarks. The sites with intracranial error-related potentials were sampled from cylindrical wells centered 29 mm anterior to the inter-aural line and either on the midline (monkeys M and F) or 5 mm lateral to the midline (monkey U). This region is coextensive with an area of the ACC that is reciprocally connected with the SEF (Huerta and Kaas, 1990) in which single units signal errors and the receipt of reinforcement (Ito et al., 2003). The sites with intracranial error-related potentials were distributed in a strip extending 7 mm laterally from the midline (Figure 4.9).

4.5 Discussion

We observed sensory, presaccadic, and error-related, but not reinforcement-feedback potentials in the SEF in macaque monkeys performing a saccade stop signal task. While there were clear sensory and perisaccadic evoked potentials at many sites in SEF, vanishingly few sites exhibited LFP modulation sufficient to control the initiation of saccades. The error-related potentials did covary with response time adjustments, however the correlation was opposite what one would predict if it were a signal that controls response times. The LFPs recorded from the SEF show some evidence of a signal consistent with conflict monitoring.

4.5.1 Event-related potentials during the stop signal task

Previous work from this lab has provided bridging evidence between human electrophysiology and monkey neurophysiology (Emeric et al., 2008; Woodman et al., 2007). Several reports have described ERPs from human subjects performing stop signal tasks (Bekker et al., 2005b; De Jong et al., 1990, 1995; Dimoska et al., 2006; Kok et al., 2004; Naito and Matsumura, 1994a; Pliszka et al., 2000; Ramautar et al., 2004, 2006b,a; Stahl and Gibbons, 2007; van Boxtel et al., 2001; Endrass et al., 2007). This body of literature suggests the following. Larger N2 and P3 components are observed in stop signal as compared with no stop signal trials and these components differ when comparing cancelled and noncancelled stop signal trials. However, ERP components have not been consistently identified that modulate before SSRT on cancelled trials and thus provide signals sufficient to control the initiation of movements.

The ERN has been observed on noncancelled trials in the saccade stop signal task (Endrass et al., 2005), but the enhanced stop-signal aligned N2 on noncancelled trials may also be identified with the ERN. An alternative hypothesis suggests that the N2 observed on cancelled trials has also been suggested as an index of the efficacy of stopping (e.g., Dimoska et al. 2006; Kok et al. 2004). However, given these conflicting accounts of the functional significance of the N2 component, it is difficult to identify the N2 conclusively with a measure of conflict or inhibition. Finally, source localization identifies the N2 and P3 components on cancelled and noncancelled trials with different parts of the brain with the medial frontal cortex among other loci contributing. Although the results presented by Emeric et al. (2008) and herein complement these observations, further investigation coordinated across species, task conditions, and effectors is required.

4.5.2 Stimulus-related and perisaccadic modulation

The LFPs in SEF were consistently polarized in the interval following the stimulus - visual and auditory - onset and in the perisaccadic interval. The visual evoked LFP modulation was observed consistently and at short latency relative to the stimulus. This is consistent with reports of SEF single-unit studies observing visual activity (Schall, 1991b; Amador et al., 2004; Pouget et al., 2005). In contrast, the LFPs in ACC are weakly polarized in the interval following the stimulus onset (Emeric et al., 2008). SEF receives many more afferents from visual areas than ACC. The SEF is innervated by MST, the superior temporal polysensory area, LIP, FEF, premotor cortex, and ACC (Huerta and Kaas, 1990) while the ACC receives few visual afferents,

mainly from area PO, area 7a in the inferior parietal lobule, and inferotemporal area TG (Van Hoesen et al., 1993), the SEF (Huerta and Kaas, 1990; Luppino et al., 1990) and a diffuse connection with FEF (Huerta et al. 1987; Stanton et al. 1993; but see Wang et al. 2004). The auditory stimulus evoked LFP modulation was observed less frequently than visually evoked LFP modulation but still at short latency relative to the stimulus. This is consistent with reports of SEF single-unit studies observing activity elicited by auditory stimuli (Schall, 1991b; Tanji and Kurata, 1982; Wise and Tanji, 1981).

The LFPs in the SEF were consistently polarized as well in the pre- and post-saccadic intervals. The correlation of the negative-going polarity preceding contraversive saccades was greater than the correlation of the positive-going polarity for ipsiversive saccades. This is consistent with SEF single-unit studies observing increased activity relative to saccade onset (Schall, 1991a; Schlag and Schlag-Rey, 1987; Hanes et al., 1995) and the readiness potential observed for visually guided saccades (Everling et al., 1996a; Evdokimidis et al., 1991). The vast majority of sites in SEF exhibited LFPs with significant postsaccadic modulation. Different subpopulations of neurons are active in the postsaccadic interval. A number of studies have also reported increased activity related to trial outcome following responses (Stuphorn et al., 2000; Schall, 1991a; Amador et al., 2000).

4.5.3 Response control

Microstimulation, anatomical data, single-unit, and lesion studies have led to a less that clear picture of the role of SEF in response control (reviewed by Schall et al.

2002; Schall and Boucher 2007). Although, eye movements can be evoked using low currents (Schlag and Schlag-Rey, 1985), lesions of SEF cause modest impairment of gaze (Schiller and Chou, 1998) Many SEF neurons are selectively active during the preparation and execution of saccades, but, in the context of the saccade stop signal task, these neurons with apparent movement related activity fail to produce signals sufficient to control gaze (Stuphorn et al., 2009).

The countermanding paradigm provides a clear criterion for determining whether neural activity generates signals sufficient to control the production of movements. The key test is whether the activity of neurons if different between trials with a movement (no stop signal or noncancelled trials) and trials with no movement (cancelled trials), and, critically, whether such a difference occurs before SSRT. If some neural modulation occurs after SSRT, then according to the race model that identifies SSRT with the time of inhibition of the movement the modulation is too late (Boucher et al., 2007b; Logan et al., 1984). Specifically, if a neural signal is to be sufficient to control movement then a significant difference in the activity on cancelled trials versus the activity on no stop trials, it must do so before SSRT (Hanes et al., 1998; Paré and Hanes, 2003).

The present analysis of the SEF field potentials, revealed vanishingly few sites with LFP modulation sufficient to control gaze. At sites with a significant LFP modulation on cancelled trials, the latency was much longer than the SSRT (Figure 4.3). This is consistent with the observation that very few movement neurons in SEF modulate their activity on cancelled trials before SSRT (Stuphorn et al., 2009). This is further evidence against SEF having a direct role in the control of gaze shifts. Human SEF

patients exhibit mild deficits in goal directed saccades (Pierrot-Deseilligny et al., 2002; Husain et al., 2003; Parton et al., 2007) and, in monkeys, lesions of SEF cause modest impairment of gaze (Schiller and Chou, 2000).

4.5.4 Performance monitoring

A dipole for the ERN can be located in the ACC (e.g., Dehaene et al. 1994; Miltner et al. 1997; van Veen and Carter 2002), but the supplementary motor area cannot be excluded as a generator of this potential (Garavan et al., 2003). Both Falkenstein et al. (1991) and Gehring et al. (1993) initially proposed that the ERN/Ne reflects a comparison between the representations of the overt error response and the correct response. An ERN-like potential has also been identified in human intracerebral EEG recording (Brázdil et al., 2002a; Brázdil et al., 2005), error-related field potentials in the medial frontal cortex of monkeys (Gemba et al., 1986), and recently in monkeys performing a saccade stop signal task (Emeric et al., 2008). The ERN was originally interpreted as an error-detection signal resulting from a mismatch between the response and the outcome of response selection (Falkenstein et al., 1990, 1991; Gehring et al., 1993). However, alternate accounts view the ERN as a brain signal reflecting detection of response conflict (Botvinick et al., 2001; Yeung et al., 2004) or representing the dopaminergic input to the ACC (Holroyd et al., 2002, 2005).

4.5.5 Response conflict

Functional imaging and event-related potential research has localized a dipole for the ERN to the ACC (e.g., Dehaene et al. 1994; Miltner et al. 1997; Carter et al.

1998), but conflict-related single-unit activity in the SEF and activation in the supplementary motor area have also been observed under conditions of response conflict as well (Garavan et al., 2003; Stuphorn et al., 2000). The absence of field potentials in the ACC signaling conflict during the saccade stop signal task is incompatible with the general conflict-monitoring hypothesis of ACC function (Emeric et al., 2008; Ito et al., 2003; Nakamura et al., 2005). The modulation of the N2 event-related potential during high-conflict trials have been emphasized as evidence for this conflict hypothesis (Botvinick et al., 2004; Yeung et al., 2004). Recall that intracranial error-related potentials occur in humans (Brázdil et al., 2002a; Brázdil et al., 2005) and monkeys (Gemba et al., 1986). Similarly, an intracranial NOGO N2 has also been observed in human SMA (Ikeda et al., 1999) and monkey PFC (Sasaki et al., 1989). According to this interpretation, the N2 and the ERN originate from the same neural process but are just observed at different times; response conflict on correct trials is supposed to precede the response and is manifested as the N2, whereas response conflict on error trials follows the response and is manifested as the ERN. In the context of the stop signal task, when stop signals occur less often, response times are faster therefore there is greater coactivation between the process that triggers the movement and the process which inhibits the movement. Consistent with the conflict hypothesis, Ramautar et al. (2004) observed that the N2 was larger and of longer latency when stop signals occur less frequently. The central tenets of the conflict hypothesis are that conflict is produced when mutually incompatible responses are active and response times increase following trials with high conflict.

We tested both of these predictions. First, the magnitude of SEF field potential

modulation did increase with the probability of noncancelled saccades (Figure 4.4). In fact, the magnitude of the modulation increased with both the stop signal delay and the probability of noncancelled saccades. This result is consistent with other studies that have observed ERPs that increase with the level of response conflict (Gehring and Fencsik, 2001; Yeung et al., 2004). However, it is inconsistent with the SEF single unit data where SEF conflict cell activity was correlated with probability of noncancelled saccades but not the increasing stop signal delay. This is inconsistent with one postulate of the conflict hypothesis which predicts that response times increase following trials with high conflict.

This is consistent with the pattern of modulation of SEF neurons signaling conflict (Stuphorn et al., 2000) but is not completely compatible with the predicted variation of response conflict in this task, which increases on cancelled trials as a function of the decreasing probability of canceling but not as a function of the stop signal delay.

Examinations of single-unit activity in the medial frontal cortex of monkeys performing the saccade stop signal task have reported distinct populations of neurons that are modulated for errors, reinforcement, and response conflict (Ito et al., 2003; Stuphorn et al., 2000). Stuphorn et al. 2000 identified single units in the SEF modulated by response conflict on cancelled trials that were not modulated on noncancelled trials as well as separate SEF neurons modulated by noncancelled errors and reinforcement. Ito et al. (2003) identified single units in the ACC modulated by errors and reinforcement but not response conflict. Field potentials, both those recorded from the scalp and intracranially, are hypothesized to be produced by standing synaptic dipoles, a signal to which action potentials may not contribute. Therefore further

work is required to examine field potentials in the medial frontal cortex for components that may contribute to conflict-related potentials recorded from the scalp.

4.5.6 Error monitoring

Converging evidence from imaging, ERPs, and intracranial field potentials have implicated the ACC as the generator of the ERN (reviewed by Bush et al. 2000). In this investigation, we consistently observed negative-going potentials followed by positive-going potentials after noncancelled errors throughout SEF in monkeys performing a saccade stop signal task. This LFP modulation was not observed when comparing correct cancelled stop signal trials to correct no stop signal trials. Therefore the LFP modulation was not evoked by the stop signal. The LFP modulation occurred after both contra- and ipsiversive errant noncancelled saccades. Therefore it is unlikely that this modulation is due to a sensory or movement-evoked potential. We therefore interpret this LFP modulation as signaling the occurrence of an error. Intracranial error-related potentials have been previously observed in the ACC of macaque monkeys (Gemba et al., 1986; Emeric et al., 2008). In addition, intracranial error-related potentials have been observed in humans that covary in time with potentials recorded at the scalp (Brázdil et al., 2002a; Brázdil et al., 2005). This evidence leads us to the conclusion that the error-related potentials observed in this study are intracranial analogs of the ERN/Ne and the Pe. Further work is required, though, to confirm that an ERN can be recorded extracranially in macaques.

The ERN was originally interpreted as an error-detection signal resulting from a mismatch between the response and the outcome of response selection (Falkenstein

et al., 1990, 1991; Gehring et al., 1993). However, a signal used for performance monitoring should somehow be used to improve performance. Is the ERN is monitoring performance only or is it also the signal used to instantiate control? In an attempt to answer this question, Debener et al. (2005) found the single-trial error-related negativity of the EEG to be systematically related to behavior in the subsequent trial. Emeric et al. (2008) examined the same relationship in the ACC intracranial error-potentials and observed the same relationship reported by Debener et al. (2005) at some sites in ACC but across all the sites there was no significant correlation between the single trial amplitude and response times on the subsequent trial. The present study examined the SEF intracranial error-potentials in this manner and found a significant correlation between the single trial amplitude and response times on the subsequent trial. However, the correlation we observed was negative — smaller amplitude error-related potentials were correlated with longer response times on the subsequent trial — and therefore incompatible with Debener et al. (2005). Although, we have consistently observed intracerebral error-related potentials in the ACC and SEF of monkeys performing the saccade stop signal task, it is not clear that this particular signal would monitor and control response times on subsequent trials. Therefore, the alternate accounts that view the ERN as a brain signal reflecting detection of response conflict (Botvinick et al., 2001; Yeung et al., 2004) or representing the dopaminergic input to the ACC (Holroyd et al., 2002) have to be explored.

Further evidence supporting this conclusion is found in the timing of the intracranial field potential relative to the human ERN. In humans performing manual stop signal tasks, an ERN is recorded that exhibits a peak negative deflection 80 ms af-

ter the error response (Kok et al., 2004; Ramautar et al., 2004, 2006b,a). Similarly, the ERN measured during an antisaccade task peaked 80 ms after error saccades (Nieuwenhuis et al., 2001). ERP components measured from the scalp are derived from LFPs distributed within some volume of tissue. We found that across individual sites, the ERN occurred as early as 10 ms after and as late as 210 ms after the errant saccade. Averaged across individual sessions, the intracranial error-related field potential began 93 ms after the errant saccade; however, in the grand average field potential, a significant negative-going polarization was measured beginning 33 ms and peaking 110 ms after the saccade. Given known conduction time differences between larger human and smaller macaque brains, these time values are very comparable.

Another line of evidence concerns the morphology of the polarization. Similar to the grand average error-related LFP reported here and by Emeric et al. (2008), the ERN waveform for saccades appears double-peaked (Nieuwenhuis et al., 2001; Van 't Ent and Apkarian, 1999). However, the response-locked ERN may overlap with the stop signal-locked N2, therefore the negative-going potentials observed following noncancelled errors may reflect both stop signal and error-related processing (e.g., Dimoska et al. 2006; Ramautar et al. 2004, 2006b,a. Thus the topographic and temporal similarity between the human ERN and the intracranial error-related negative-going field potential in the macaque SEF suggests that the intracranial potential contributes to the dipole producing the surface potential.

The error-detection hypothesis originally included the premise that ERN magnitude relates to response time adjustments (Coles et al., 1995; Gehring et al., 1993). Several studies have examined this relationship with diverse results using ERPs

(Debener et al., 2005; Gehring and Fencsik, 2001; Gehring et al., 1993; Scheffers et al., 1996) and fMRI (Debener et al., 2005; Garavan et al., 2003). We found that the variations in response time adjustment covaried with the magnitude of negative-going, but not the positive-going, error-related field potential modulation on the preceding noncancelled trial similar to other recent studies of human subjects (Gehring and Fencsik, 2001; Nieuwenhuis et al., 2001). However, the magnitude of the negative-going error-related potential decreased with increasing response time, which is inconsistent with a signal that should lead to longer response times. The general interpretation of these results should acknowledge that response times do not increase systematically following noncancelled saccade errors (Cabel et al., 2000; Emeric et al., 2007), and the overwhelming majority of these saccades are not followed by an immediate corrective saccade back to the initial fixation (Ito et al., 2003). Thus it is possible that medial frontal error signals are not used to control response times in subjects performing the saccade stop signal task and are instead a generic monitor of the occurrence of errors (e.g., Holroyd et al. 1998).

4.5.7 Reinforcement learning

The reinforcement learning hypothesis proposes that the frontocentral negativity is elicited by events signaling error, loss of reinforcement, or punishment (e.g., Gehring and Willoughby 2002b; Miltner et al. 1997). Holroyd et al. (2002) hypothesize that the mesencephalic dopamine system conveys a negative reinforcement learning signal to the frontal cortex when human participants commit errors in reaction time tasks. They also proposed that errors induce phasic changes in mesencephalic dopaminergic

activity that is manifest through ACC activity producing the ERN. Consistent with this, single units in ACC that discharge after errors are also active when earned reinforcement is withheld (Ito et al. 2003; see also Niki and Watanabe 1979). Also in monkeys performing the saccade stop signal task, other neurons in ACC modulate in a manner directly paralleling dopamine neurons (Ito et al., 2003). In other words, single units in the ACC signal whether ongoing events are better or worse than expected.

Emeric et al. (2008) observed error-related and reinforcement-feedback potentials in the dorsal bank of the ACC in macaque monkeys performing a saccade stop signal task. Consistent with the single-unit data, Emeric et al. (2008) observed feedback-related modulation on correct no stop signal trials when reinforcement was withheld. We did not, however, observe feedback-related modulation in the SEF LFPs. Further examination is required to test whether these LFPs are modulated in a way consistent with the reinforcement learning hypothesis. This is however inconsistent with the observation that the activity of some SEF single units is predictive of reward (Amador et al., 2000; Stuphorn et al., 2000).

4.5.8 Source localization

The ERN has a frontocentral distribution over the scalp such that a dipole for the ERN can be located in the ACC (e.g., Dehaene et al. 1994; Miltner et al. 1997; van Veen and Carter 2002). However, being an inverse problem (Helmholtz, 1853), an effectively infinite number of dipoles can account for a given scalp potential topography. Intracranial recordings can contribute useful data to constrain the range of plausible solutions. Emeric et al. (2008) found prominent, mostly biphasic, LFPs

resembling human scalp ERN/Pe potentials at 70% of the sites in the monkey ACC after noncancelled errors on stop signal trials. Similarly, we observed mostly biphasic, LFPs resembling human scalp ERN/Pe potentials in the monkey SEF after noncancelled errors on stop signal trials. However, compared to ACC, the SEF LFPs herein were encountered less frequently and smaller amplitude despite identical tasks and methods. We cannot rule out volume conduction The results of this study are consistent with previous reports of error-related field potentials in the medial frontal lobe of macaques (Gemba et al., 1986; Emeric et al., 2008). In addition, intracranial ERPs resembling scalp Ne/Pe potentials have been observed in ACC as well as several other cortical locations after incorrect trials in humans (Brázdil et al., 2002a; Brázdil et al., 2005).

These observations must be viewed with appropriate skepticism though. Although the ACC is the structure most often activated in response to errors, response conflict, and reinforcement, many other structures are activated in the same context (reviewed by Hester et al. 2004). Furthermore, the variability of the activation patterns within the cingulate of subjects performing cognitively demanding tasks further limit conclusions regarding the subdivisions of the cingulate actively involved in performance monitoring (Hester et al., 2004; Fujiwara et al., 2009). The morphological variability of the human brain may contribute to this uncertainty. For example, the negativity of the potential field associated with the equivalent dipole lies above the apical dendrites of the pyramidal cells. The ERN/Ne is a negativity with a frontal central distribution and its equivalent dipole is inferred to be oriented parallel to the pyramidal cells. This implies that the cortical layer that generates the ERN/Ne must

run parallel to the area of the scalp where the ERN/Ne is maximal. Therefore the negative pole of the equivalent dipole must point in this direction, where the scalp activity reaches a maximum. In the human brain, $30-50\%$ of the human population posess a second cingulate sulcus, the paracingulate (Paus et al., 1996b,a; Pujol et al., 2002). In humans with just a cingulate sulcus, Brodamann's area 24c lies in the depths of the ventral bank of the cingulate sulcus while the SMA lies on the medial wall — perpendicular to the scalp (Vogt et al., 1995). In humans with a paracingulate sulcus that extends caudally to the supplementary motor area, portions of the SMA are parallel to the scalp and may contribute to the equivalent dipole of the ERN.

Due to superposition, potentials generated by local and remote sources and sinks add algebraically at any given point so interpreting field potentials entirely in terms of local generators is uncertain. Thus it is possible that the field potentials Emeric et al. (2008) observed in the dorsal bank of the ACC arose from dipoles in, for example, the ventral bank of the ACC or more dorsally in the SEF. Evidence against this concern, though, includes preliminary results we have obtained showing attenuated or absent error-related field potentials in the ventral bank of the ACC (Emeric et al., 2003) and the current result that error-related potentials are less commonly observed in the SEF. Moreover, the magnitude of the grand average error-related potentials in ACC is an order of magnitude greater in ACC than SEF. Nevertheless, to resolve this localization problem most definitely, it will be necessary to record current source density across the medial frontal cortex, spanning the layers of the dorsal and ventral banks of the ACC and SEF (e.g., Dias et al. 2006).

4.5.9 Supplementary eye fields and gaze control

The anatomical and physiological evidence has led to the hypothesis that the SEF's is a node in an interconnected network of brain areas involved in the generation of eye movements (reviewed by Platt et al. 2004). The SEF can influence activity in the superior colliculus indirectly via its projections to the caudate (Selemon and Goldman-Rakic, 1985; Arikuni and Kubota, 1986; Shook et al., 1991). The SEF might also influence performance indirectly through its dense and reciprocal connections with the FEF (Schall et al., 1993; Stanton et al., 1993; Huerta and Kaas, 1990), prefrontal area 46 (Huerta and Kaas, 1990), the ACC (Huerta and Kaas, 1990; Luppino et al., 2003), and its projections to the caudate (Selemon and Goldman-Rakic, 1985; Arikuni and Kubota, 1986; Shook et al., 1991). Both FEF and area 46 project directly to the intermediate layers of the superior colliculus (Leichnetz et al., 1981), while the ACC can subtly influence the ocular motor system via its projections to the locus coeruleus (reviewed by Aston-Jones and Cohen 2005) and its oligosynaptic connection to extraocular motoneurons (Moschovakis et al., 2004). While the SEF is connected to many of the same ocular motor structures these connections are less dense and less focal than the FEF connections which suggest that SEF may influence gaze control in a more subtle manner.

Previous work has shown that subthreshold microstimulation of the SEF affects stop signal task performance in monkeys by delaying saccade initiation (Stuphorn and Schall, 2006) and preliminary evidence from the same paradigm applied to ACC suggest that ACC does not directly influence saccades (Emeric 2008 soc neuro ab-

str).Finally, Aron et al. (2006) have emphasized a critical role of the subthalamic nucleus in response inhibition during a manual stop signal task. The subthalamic nucleus is innervated by the FEF and SEF but not the rostral portion of the ACC (e.g., Frankle et al. 2006; Huerta and Kaas 1990; Huerta et al. 1986). Much more work is needed to determine the relative contributions of each of these pathways in the executive control of gaze.

4.5.10 Event related LFPs while countermanding saccades: SEF versus ACC

The results of this study can be directly compared to Emeric et al. (2008). Taken all together, the results of these studies suggest slightly different roles for SEF and ACC in the initiation and control of saccadic eye movements. First, the stimulus-aligned LFPs in SEF onset earlier and are clearly more polarized than the LFPs in ACC. In the interval preceding the saccade, the SEF LFPs were more polarized than the ACC LFPs and this polarization was frequently observed in the SEF but less often in the ACC. Neither SEF nor ACC LFPs produced signals sufficient to control gaze. The pattern of SEF LFP polarization was consistent with that predicted by the conflict monitoring hypothesis this was not observed in ACC. The incidence of postsaccadic polarization was not different between SEF and ACC. However, the incidence and amplitude of error-related potentials was greater in ACC than SEF. Finally, while Emeric et al. (2008) observed reinforcement-related LFPs in ACC, we report the absence of such modulation in the SEF LFPs. Akkal et al. (2002) report similar findings in the context of a visually instructed, delayed sequential movement task. As in this study, the main difference between the pre-SMA and the cingulate

was the abundance of responses to visual stimuli in the pre--SMA (see also Amador and Fried 2004), while cingulate activity was more related to reward. Taken all together, the results suggest that, despite sharing functional properties, the two areas participate in different aspects of motor behavior: the SEF integrates external stimuli while the ACC monitors internal states during motor planning.

4.6 Conclusion

The results of this study and Emeric et al. (2008) are measures of field potentials in the medial frontal cortex of monkeys performing a saccade countermanding task which exhibit patterns of modulation consistent with accounts of the functional significance of the ERN. Such hypotheses ultimately require measurements of single units and field potentials that can be compared with the surface field potentials. The hypotheses regarding the functional significance of the ERN ultimately require measurements of single units and field potentials that can be compared with the surface field potentials. Finding intracranial homologues of the ERN is a necessary bridge.

This study provides further evidence of an analog of the ERN in the SEF field potentials of monkeys performing a stop signal task. Electrophysiological studies have led to the current view that electrical potentials recorded at the scalp are the result of summed cortical LFPs, which are generated by the synchronous synaptic activity of populations of neurons across the brain. Finding error-related field potentials concomitantly with unit activity in the ACC and SEF provides converging evidence between the human ERN literature and the monkey neurophysiology literature. These findings provide an avenue for more closely examining the neural events that give rise

to human ERPs.

4.6.1 Acknowledgemnts

We thank E. Crowder, A. Garr, and M. Feurtado for help with animal care.

4.6.2 Grants

This work was supported by National Institutes of Health Grants F32-EY-017765, T32-MH-065782, R01-MH-55806, P30-EY-08126, and P30-HD-015052 and by Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience.

CHAPTER V

EVENT-RELATED POTENTIALS MEASURING ERROR DETECTION AND PERFORMANCE MONITORING IN NONHUMAN PRIMATES

5.1 Abstract

Event-related potentials (ERPs) recorded from humans have been critical in shaping theories of executive control and performance monitoring. Here, we show that ERPs recorded from macaque monkeys performing a countermanding task (i.e., the stop-signal paradigm) evidence an error-related component similar to that found in humans. Monkeys were cued to make a visually guided saccade that was supposed to be cancelled if an imperative stop signal appeared. During the countermanding task, the most prominent feature was a frontocentral positivity following unrewarded errors compared to rewarded correct trials. This error-related positivity could not be explained by low level visual stimulus processing. These findings establish a bridge between neurophysiological studies of performance monitoring in humans and nonhuman primates.

5.2 Introduction

Converging evidence from human and nonhuman primates studies implicates the medial frontal cortex as having a central role in performance monitoring (Reviewed by Paus 2001; Passingham et al. 2010; Posner et al. 2007; Schall and Boucher 2007). The first electrophysiological correlate of performance monitoring in humans, the

error related negativity (ERN/Ne), was reported by Falkenstein et al. (1990) and Gehring et al. (1993). This frontocentrally distributed negative going potential peaks ∼100 ms following error responses and the dipole source of the ERN and functional activation in response to errors is most consistently observed in the medial frontal cortex (e.g., Menon et al. 2001; Dehaene et al. 1994; van Veen et al. 2001; Miltner et al. 1997; Reviewed by Hester et al. 2004).

Since the discovery of this event-related potential (ERP) component, investigations regarding performance monitoring have converged on the medial frontal cortex, the ERN, and the functional significance of this ERP component (e.g., Botvinick et al. 2001; Holroyd and Coles 2002). Investigations have typically used speeded, performance demanding tasks such as the Eriksen flanker task, the Stroop task, variants of the GO/NOGO task, and the countermanding (i.e., stop signal) task. One of the first observations suggesting the ERN monitors performance was that emphasizing speed, at the expense of accuracy, diminished the amplitude of the ERN (Falkenstein et al., 2000; Gehring et al., 1993). The past decade of research has established the ERN as one of the key ERP components indexing monitoring and adjustments of flexible, goal-directed behavior (reviewed by Taylor et al. 2007).

Consistent with previous reports of the ERN during speeded response tasks, the ERN has been observed during the countermanding task (Endrass et al., 2005; Krämer et al., 2007; Liotti et al., 2005; Stahl and Gibbons, 2007; van Boxtel et al., 2005; Vocat et al., 2008) and a dipole source of the ERN in this task has also been localized to the medial frontal cortex (van Boxtel et al., 2005; Vocat et al., 2008). The role of the medial frontal cortex in performance monitoring has been further supported by the

observation of single units and intracranial local field potential that are modulated after errors, response conflict, and the absence of rewards during a saccade stop signal task (Emeric et al., 2008, 2010; Ito et al., 2003; Stuphorn et al., 2000, 2010; Scangos and Stuphorn, 2010).However, species and methodological differences weaken the conclusions that can be drawn. The presence of a component similar to the ERN in monkeys would provide leverage for rigorously testing models of the functional significance of the ERN using simultaneously acquired single units, intracranial LFPs, and ERP methods in nonhuman primates (e.g., Cole et al. 2009).

The present study reports the characteristics of surface event related potentials from macaque monkeys performing the saccade countermanding (stop signal) task. We used a variety of referencing configurations and task manipulations to verify the robustness of the findings. In particular, the human ERN has a broad frontocentral distribution and this means that a monkey homologue of this component should be observable whether we use reference sites similar to those in studies of humans (i.e., mastoids or earlobes) or those in previous monkey ERP studies. The location of the reference electrode(s) can change the pattern of voltage recorded across the head but not the timing of effects (Luck, 2005; Nunez and Srinivasan, 2006). An additional motivation for exploring the effects of using a variety of electrode configurations was to provide more precise voltage distribution maps and to rule out that any effects we observed were due to artifacts of the visual stimulation being different between correct and error trials. The variations in the behavioral tasks were used to establish the boundary conditions for observing the error-related activity and to maximize the number of error trials within each session to improve the signal-to-noise ratio for

recording the ERPs. To foreshadow the findings, we first established that we could observe presaccadic spike potentials and visual ERP components elicited by retinal image motion following the saccade that are well known in ERP studies of humans. The results provide clear evidence that macaque monkey ERPs signal the detection of errors. Some of the findings have appeared previously in abstract form (Garr et al., 2008).

5.3 Methods

Data were collected from one male bonnet (F, *Macaca radiata*: 8 kg) and 1 female rhesus macaque (Y, *Macaca mulatta*: 7 kg) that were cared for in accordance with U. S. Department of Agriculture and Public Health Service Policy on the humane care and use of laboratory animals. The animals were tested for ∼3-5 h/day, 3-5 day/wk. During testing, water or fruit juice was given as positive reinforcement. Access to water in the home cage was controlled and monitored. Fluids were supplemented as needed. Detailed descriptions of all surgical procedures, electrophysiological techniques, behavioral training, and tasks have appeared previously (Hanes and Schall, 1995; Hanes et al., 1998; Woodman et al., 2007).

The experiments were under computer control to present stimuli, record eye movements, and deliver liquid reinforcement. Stimuli were presented on a video monitor (48 x 48°) using computer-controlled raster graphics (TEMPO Videosync 1280 x 1040 resolution). The fixation spot subtended 0.37° of visual angle, and the target stimuli subtended from 0.3 to 3° of visual angle, depending on their eccentricity and had a luminance of 10 or 30 cd/m^2 on a 1 cd/m^2 background. Eye position was monitored

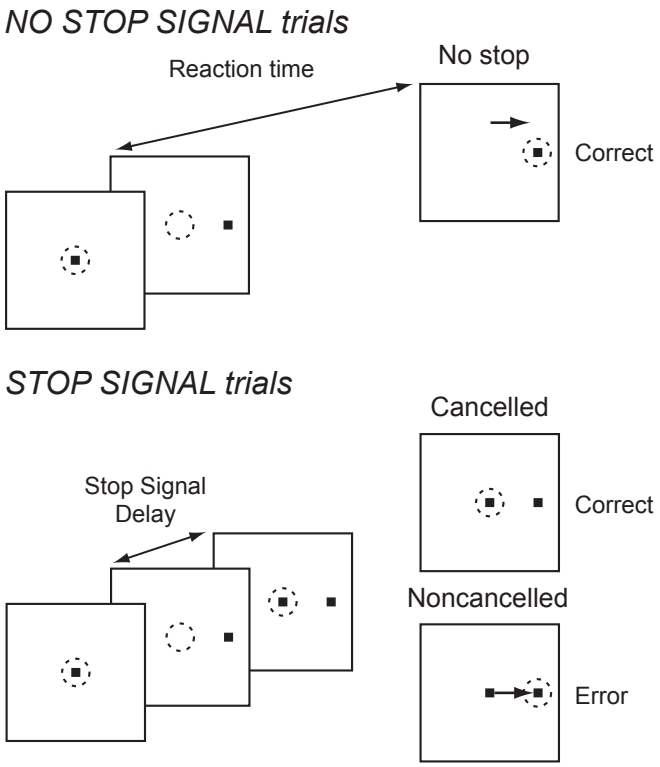

Figure 5.1: Trial displays for saccade countermanding task. Dotted circle indicates focus of gaze at each interval; arrow, the saccade. All trials began with presentation of a central fixation spot. After fixation of this spot for a variable interval, it disappeared simultaneous with presentation of a target on the left or right. In no stop signal trials, a single saccade to the peripheral target was reinforced as the correct response. In stop signal trials, the fixation spot reappeared after a variable stop signal delay. Maintained fixation was reinforced as the correct response; these are referred to as cancelled (or signal-inhibit) trials. If a saccade was produced in spite of the stop signal, no reinforcement was given; these errors are referred to as noncancelled (or signal-respond) trials.

via a video-based infrared eye tracker (ASL, Bedford, MA) while monkeys were head-restrained and seated in an enclosed chair within a magnetic field. Saccades were detected using a computer algorithm that searched for significantly elevated velocity (30°/s). Saccade initiation and termination were detected offline using custom MATLAB scripts and defined as the beginning and end of the monotonic change in eye position during the high-velocity gaze shift.

The countermanding task provided the data for this study. All trials began when the monkey shifted gaze to fixate a centrally located stimulus for a variable interval (400-1100 ms; Figure 1.1). Following this fixation interval, the central stimulus was removed and simultaneously a peripheral target was presented at one of two locations in opposite hemifields cuing the monkey to make a single saccade to the target. Targets were located along the horizontal axis and (10°) from the fixation target in the vast majority of sessions. For trials with no stop signal, monkeys were reinforced for making a saccade within 700 ms. In each behavioral session, the delay between fixation of the target and delivery of reinforcement was constant at 600 ms. On 20-75% of the trials, after a delay, referred to as the stop signal delay (SSD), the central fixation target reappeared, instructing the monkey to inhibit saccade initiation. Two outcomes were possible on these stop signal trials. Maintaining fixation on the stop signal for 700 ms after the target appeared was reinforced as correct; these trials were referred to as cancelled trials. On stop signal trials, a saccade to the target was considered incorrect, and thus resulted in a 1500 ms timeout with no reinforcecment. These trials were referred to as noncancelled trials. In each behavioral session, four to nine SSDs of constant value ranging from 0 to 480 ms were used. SSDs were varied according to the monkeys' performance so that at the shortest SSD, monkeys generally inhibited the movement in $> 75\%$ of the stop signal trials and at the longest delay, monkeys inhibited the movement in $< 25\%$ of the stop signal trials. SSDs could be distributed uniformly or adjusted dynamically using a tracking procedure (e.g., Band et al. 2003b). The values were adjusted across sessions and monkeys to adjust for overall changes in response time so that, on average, monkeys failed to inhibit

approximately half the stop signal trials.

5.3.0.1 EEG electrodes

The electrode implants were constructed from Teflon-coated braided stainless steel wire and solid-gold terminals. Implanted wires were cut to 8.5 cm, the wire ends exposed, and gold amphenol pins were crimped to both ends. One end of the wires were inserted into a plastic connector, whereas the gold pin crimped on to the other end was ground down until $\sim$1 mm of the pin remained. During aseptic surgery, 1 mm deep holes were drilled into the surface of the skull, allowing the terminal end of the electrode to be tightly inserted. The inserted gold pin was then covered with a small amount of acrylic cement. After all of the EEG electrodes were implanted, the plastic connector was attached to exposed acrylic to allow access to the channels. The electrode leads that were not embedded in the acrylic were covered by skin that was sutured back over the skull, allowing for the EEG electrodes to be minimally invasive once implanted. Unlike recordings from skull screws that extend to the dura mater through the skull (e.g.,Vezoli and Procyk 2009), recordings from these electrodes approximate those used in human electrophysiological studies because the signals must propagate through the layers of brain, dura, and skull.

The impedance of the EEG electrodes once implanted was $2-5$ kΩ measured at 30 Hz, just as those of low-impedance EEG electrodes typically used in human studies. We implanted 8 and 6 electrodes in monkeys F (on 2 separate occasions) (Figure 5.2A and B) and 16 in monkey Y (Figure 5.2C) spanning the frontal, parietal, and occipital bones. We initially implanted eight electrodes in monkey F approximating sites F3,

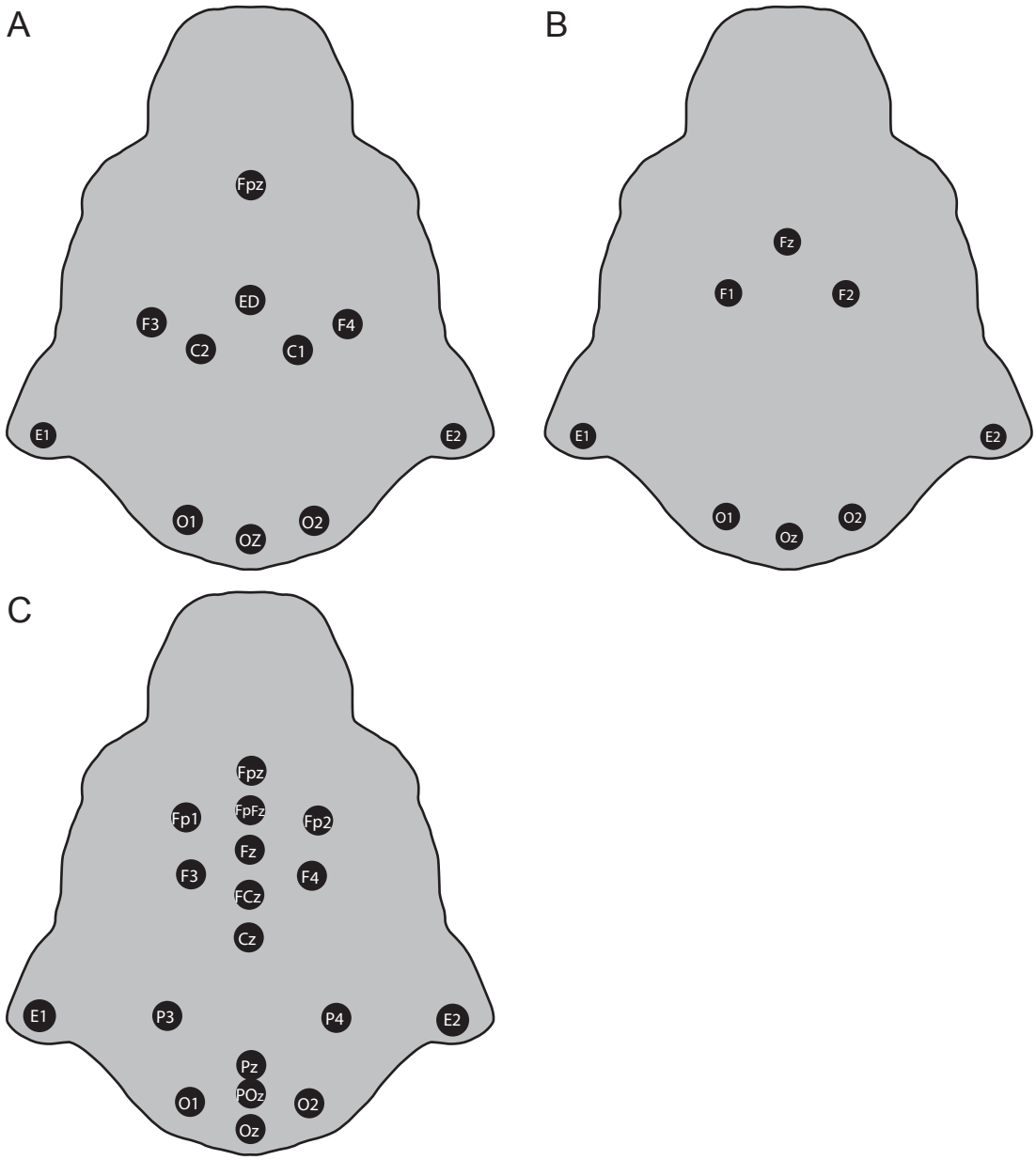

Figure 5.2: Names and positions of the modified 10-20 system. (A) Monkey F was initially implanted with 8 surface electrodes. A single epidural electrode is also represented (ED), which we refer to as FCz due to its position. (B) Monkey F was later implanted with 6 surface electrodes and one epidural electrode. (C) Monkey Y was implanted with 16 electrodes.

F4, C1, C2, O1, O2, and Oz of the modified human 10/20 system (Woodman and Luck, 2003; Jasper, 1958; Woodman et al., 2007). The frontal-most electrode site, FPz, was placed immediately behind the brow ridge (stereotaxic coordinates: 56 mm anterior, 0 mm lateral/medial). During a surgery to repair the implant, FPz, F3, F4, C1, and C2 were removed and electrodes located at FpFz* and F3-4 were implanted adjacent to the existing implanted chambers on monkey F leaving 6 electrodes. Note that FpFz* was located on the midline midway between FpFz and Fz in this particular electrode configuration for monkey F (Figure 5.2B). Electrocorticographical signals (ECoG) were simultaneously recorded by placing 23 gauge stainless steel wire into the grid holes along the midline such that they were touching the dura. These wires were connected to the preamp via amphenol connectors. In monkeys X and Y, surface electrodes were implanted using a template for the $10-20$ system (Jasper, 1958) in stereotaxic coordinates which was created using a *Macaca mulatta* skull (Skulls Unlimited International, Inc., Oklahoma City, OK). Sixteen and twenty-five surface electrodes were implanted using this method in monkeys X and Y, respectively (Figure 5.2C and D).

5.3.1 Data acquisition

ERPs were recorded using implanted surface electrodes (impedance: $2-5$ KΩ at 1 kHz), nonreferenced single ended. The electrode signals were amplified with a high-input impedance head stage ($>$ 1 GΩ , $\sim$2 pF of parallel input capacitance. Plexon Inc. HST/8o50-G1-GR) and filtered by a Multichannel Acquisition Processor (Plexon, Dallas, TX). The ERP data were filtered between 0.7 and 170 Hz with two

cascaded one-pole low-cut Butterworth filters and a four-pole high-cut Butterworth filter and was sampled at 1 kHz.

The location of the reference electrode(s) can change the pattern of voltage recorded across the head but not the timing of effects (Luck, 2005; Nunez and Srinivasan, 2006).We examined the effects of using a variety of electrode configurations to provide more precise voltage distribution maps and to rule out the possibility that any effects we observed were due to artifacts of the visual stimulation being different between correct and error trials. The ERPs were referenced to either implanted electrodes (e.g., midline occipital, Oz or linked mastoids, M1 and M2) or tin cup electrodes attached to the skin at mastoid bone or medial aspect of the ear which were connected to the same ground wire on the head-stage (Figure 5.2). Monkeys F and Y were not implanted with mastoid electrodes. The tin cup electrode clips were attached to ears and filled with electrode paste. Plain tin cup electrodes were attached to the mastoids with adhesive and filled with electrode paste. There was no systematic difference in impedance at the signal electrodes for ear versus mastoid referencing. The impedance changed at individual electrodes a maximum of $\pm 0.02\,\mathrm{k}\Omega$ between referencing the ears versus the mastoid electrodes that were attached with adhesive.

5.3.2 Data analysis

Behavioral and ERP analyses were performed offline using custom Matlab scripts. All EEG signals were assessed for the occurrence of excessive noise and reoccurring artifacts. Single trials ERPs with voltage exceeding 300μV during time intervals of

interest were excluded from further analysis. No selection was made on the basis of whether or not the ERPs displayed task-related polarization. The mean voltage in the 350 ms to 50 ms period preceding the saccade initiation for each valid trial was defined as the baseline and subtracted from the voltage for each trial. The ERPs were baseline corrected but unfiltered beyond the amplifier bandpass settings because of the power inherent in the large number of trials obtained (> 3500 per monkey).

For each behavioral session, trials were grouped into no stop and noncancelled trials and the activity from trials of each type was time-locked relative to saccade initiation and averaged millisecond-by-millisecond. For saccade-aligned ERPs, all data after the subsequent saccade initiation and preceding it by 50 ms were discarded. This was done to ensure that the data contributing to the averages were not contaminated by presaccadic spike potentials (e.g., Ignocheck et al. 1986; Balaban and Weinstein 1985; Thickbroom and Mastaglia 1986). The grand average ERP for each trial type is the average of the session ERPs weighted by the number of trials in each session (see Data Selection for details on grouping).

Intervals of significant ERP modulation across different trial types were identified using the criterion adopted by Emeric et al. (2008).Briefly, a difference wave was produced by subtracting the saccade-aligned error noncancelled ERP from the saccade-aligned correct no stop ERP. For all comparisons between trial types, the onset of a significant difference was defined as the instant the difference wave exceeded $\pm$2SD for $\geq$ 50 ms and achieved a difference of $\pm$3SD during that interval. This criterion was used to compare the saccade-aligned ERP on trials with no stop signal to the ERP on cancelled and noncancelled trials.

For monkey Y, we produced a topographic voltage map from the difference wave (error noncancelled ERP minus correct no stop ERP) in the 100-200 ms time interval following the response at each of the implanted surface electrodes. The brain was reconstructed using a semi-automatic segmenation process implemented in BrainVoyager (Brain Innovation, Maastricht, The Netherlands). Stereotaxic coordinates for electrodes, including those at prominant landmarks (e.g., Fpz at the central indintation on the brow ridge between orbitals) were visualized in the MRI data, rescaled to voxel based coordinates, and co-registered with anatomical MRI data. Spline interpolation was used to estimate votage between electrode locations and construct 3 dimensional topgraphic maps in MATLAB. The vertices of these topographic maps were then co-registered to the corresponding electrode locations and overlayed onto the anatomical MRI reconstructions.

5.3.3 Data selection

This report is based on physiology and behavior data from 40 sessions (F, 22 sessions; Y, 6 sessions). Several parameters were varied across sessions in order to test their contribution to the observed ERP differences or to encourage better behavioral performance. In a subset of sessions, a negative feedback tone was presented on noncancelled trials the instant a gaze shift was detected. In these sessions, if the noncancelled response time was less than the stop signal delay, the stop signal was not presented. If the noncancelled response time was greater than the stop signal delay, the stop signal and the peripheral target were extinguished. These conditions are consistent with those of Stuphorn et al. (2000), Ito et al. (2003), and Emeric

et al. (2008). This contingency was adopted to eliminate confounding ERPs evoked by visual and auditory stimuli in the immediate post response period. Other session to session differences in user defined parameters included fixation holdtime distribution (aging vs. non-aging foreperiod), target holdtime, SSD range, percentage of stop trials, and SSD distribution (staircase or random). For each monkey, data from individual sessions were grouped based on the following parameters: (1) reference electrode, (2) feedback contingencies, (3) fixation holdtime distribution, (4) target holdtime, and (5) the percentage of stop signal trials. Holdtime refers to the duration of time which the monkey had to maintain gaze on either the central or peripheral target before the next phase of the task could be triggered. Individual sessions were also excluded from the database based on the quality of the electrophysiological signals (signal/noise ratio), the number of trials of each type (no less than 30 trials), and task performance. The quality of task performance was assessed using the following criteria: (1) the inhibition function had to occupy the majority of its maximum range ($0.25 \leq$P(noncancelled)≤ 0.75) and (2) the mean noncancelled response time had to be less than the mean no stop response time. The resulting subsets of sessions for monkey F and monkey Y are summarized in Table 1 and Table 2, respectively.

Compared to monkeys F and Y, monkey X was naive to the task and none of her sessions individually met the behavioral criteria. An allowance was made for monkey X to include sessions with < 30 noncancelled trials since this subject was allowed to complete short sessions with frequent breaks. Since all data are presented collapsed across sessions, and no analyses are carried out at the single session level, this presents no confound. For each of these subsets of sessions, we produced ERPs collapsed across

Table 5.1: Data selection for monkey F

Figure	4	5	6	8
Sessions(N)	15	2	3	2
Reference electrode	Oz	E1	E1	L
Feedback contingency	+	+	+	-
Hold target time(ms)	600	600	600	600
Foreperiod	Aging	Non-aging	Non-aging	Non-aging
SSD tracking	+	++	++	++
Stop Fraction (%)	20-60	50	50,60	50,70
Electrodes (N)	7	9	6	6

E1, Left ear. L, Linked ear reference.
±,negative feedback present or absent.
+/++, staircased single steps or multiple steps.

Table 5.2: Data selection for monkey Y

Figure	7	9
Sessions(N)	1	5
Reference electrode	E1	L
Feedback contingency	+	-
Hold target time(ms)	600	600
Foreperiod	Non-aging	Non-aging
SSD tracking	++	++
Stop Fraction (%)	60	30,35,40
Electrodes (N)	16	16

E1, Left ear. L, Linked ear reference.
±,negative feedback present or absent.
+/++, staircased single steps or multiple steps.

sessions to assess the effect of each of these parameters on the resulting physiology.

5.4 Results

In humans, the ERN has been consistently described as a frontocentrally distributed negative going potential occurring $\approx$ 100 ms following error responses (Falkenstein et al., 1990; Gehring et al., 1993), including errors of saccade inhibition (Endrass et al., 2005). The primary goal of this study was to determine if ERPs associated with performance monitoring exist in monkeys by comparing the response-aligned ERPs on correct no stop trials to those on error noncancelled trials. First, though, we will describe the potentials observed immediately before and after saccadic eye movements.

5.4.1 Saccade-related potentials

Rotation of the eye's electrostatic potential distorts the signal at electrodes around the orbits (Lins et al., 1993a). In humans, saccades evoke two separate potentials which can propagate to the EEG across the scalp. Saccades are preceded by extraocular muscle activity, which propagates to the EEG as a saccadic spike potential (Thickbroom and Mastaglia, 1986; Weinstein et al., 1991) and followed by what has been described as a λ response which is largest at occipital sites (Thickbroom et al., 1991; Kazai and Yagi, 2003). The spike potential in humans is largest at frontal electrode sites and peaks 40-60 ms prior to the onset of the saccade (Weinstein et al., 1991). The λ-wave consists of a saccade initiation component with positive components at $\sim$ 60 and $\sim$ 100 ms after saccade initiation, and a saccade offset component

with a positive potential at $\sim$ 80 ms after saccade offset (Thickbroom et al., 1991). Figure 5.3 plots saccade-aligned ERPs exhibiting both the spike potential (black arrows) and λ-wave (light and dark gray arrows, respectively) for leftward and rightward saccades. At frontal electrode sites, the spike potential onset and peak occurs 30 ms and 15 ms prior to the saccade initiation. At occipital electrode sites, the spike potential is a much smaller positive deflection that peaks with identical onset and peak times. For frontal electrodes ipsilateral to the saccade, there is a positive going potential following the spike potential. For frontal electrodes contralateral to the saccade, this potential is negative. At occipital electrodes, the spike potential is positive going and reduced in amplitude relative to the frontal SP. The λ-wave is largest at the occipital electrodes with saccade initiation and offset components.

Identifying these potentials validates the technique used to acquire the ERPs and justifies the subsequent analyses. In all the sessions contributing to this study, the central and peripheral targets were 10° of visual angle apart. The saccade-aligned ERPs were aquired from trials that have saccades of approximately the same amplitude, direction, and duration; therefore, the large amplitude potentials evoked by eye movements are of equal amplitude in both conditions (error noncancelled and correct no stop) and therefore cancel out.

5.4.2 Saccade-aligned ERPs: Error versus Correct

We originally referenced ERP recordings to electrode Oz for two reasons: (1) Fpz was the only frontal midline electrode implanted and (2) it would guarantee that our reference location would be as far as possible from the frontomedial electrode where

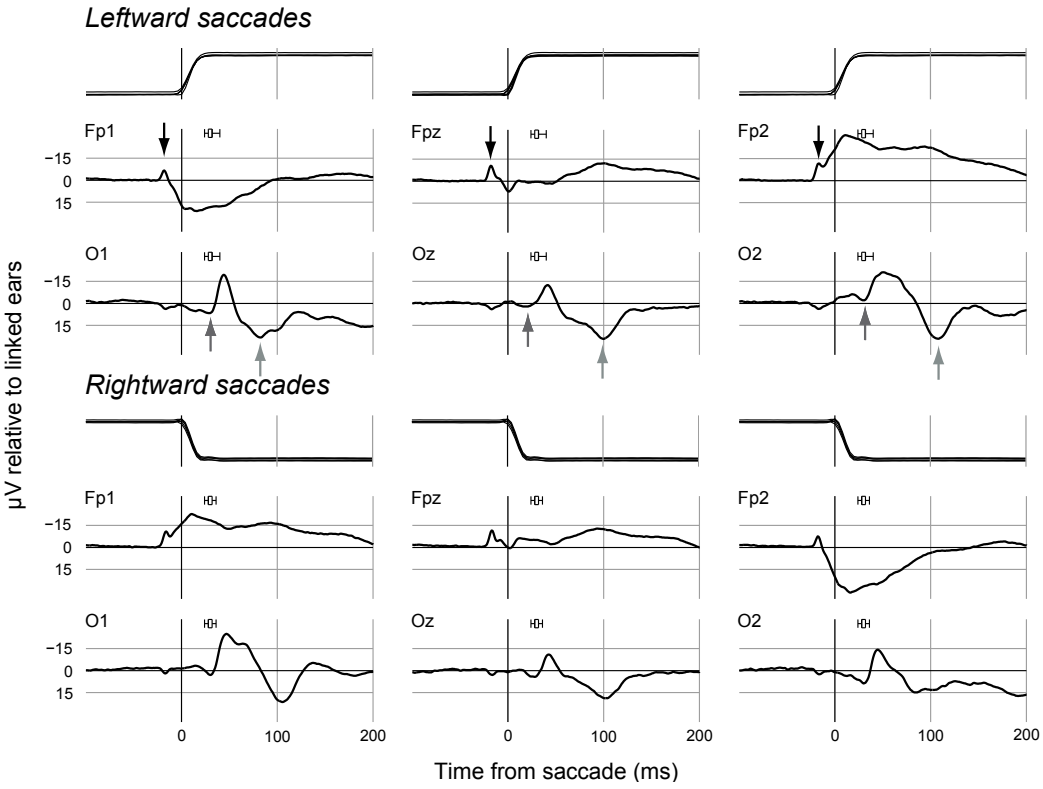

Figure 5.3: recorded from the frontal and occipital electrodes for leftward (top) and righward (bottom) 10 degree saccades. Top row of plots in each panel, the average eye position relative to saccade onset for each session contributing to the ERPs below. EEG signals are referenced relative to linked ears. Green and red box-whisker plots show the offset of the task saccade for no stop trials. Saccade synchronized ERPs are the average of 1373 (leftward) and 1877(righward) no stop signal saccades across 5 sessions.

we expected to observe error-related components. Figure 4 plots comparisons of the saccade-aligned ERPs from monkey F on noncancelled trials and no stop signal trials collapsed across targets and referenced to Oz (see Table 5.1). The middle inset plots the stereotaxic location of the ERP electrodes on a diagram of a monkey head. Active electrodes and the common reference are represented by black and white circles, respectively. Blue box-whisker plots show the latency of the subsequent task irrelevant saccades relative to the response saccade. Recall that the single trial ERPs were truncated 50 ms before the subsequent task irrelevant saccade initiation (see Methods). Green and red box-whisker plots show the termination of the task saccade for no stop and noncancelled trials, respectively. Gray fill indicates periods of significant difference between correct and erroneous responses; dark gray indicates positivity, light gray indicates negativity (see Methods). There is no difference in the duration of the saccade to the peripheral target for error noncancelled (red box-whisker plots) versus correct no stop signal saccades (red box-whisker plots). Significant positive polarization differences evolved at frontal electrodes and central electrodes F3-4 and C1-2 $\sim$ 100 ms after saccade initiation. Significant negative polarization differences evolved at electrode F4 simultaneously with saccade initiation and at O1 $\sim$ 100 ms after saccade initiation. At Fpz and F3, significant negative polarization differences evolved at 100 ms and 300 ms after saccade initiation. Consistent with our hypothesis, the saccade related components observed in Figure 5.3 at the occipital electrodes (O1-2) are attenuated in Figure 5.4. However, since EEG measures the difference between each electrode and a common reference, an argument could be made that this referencing scheme resulted in visually evoked components associated with the

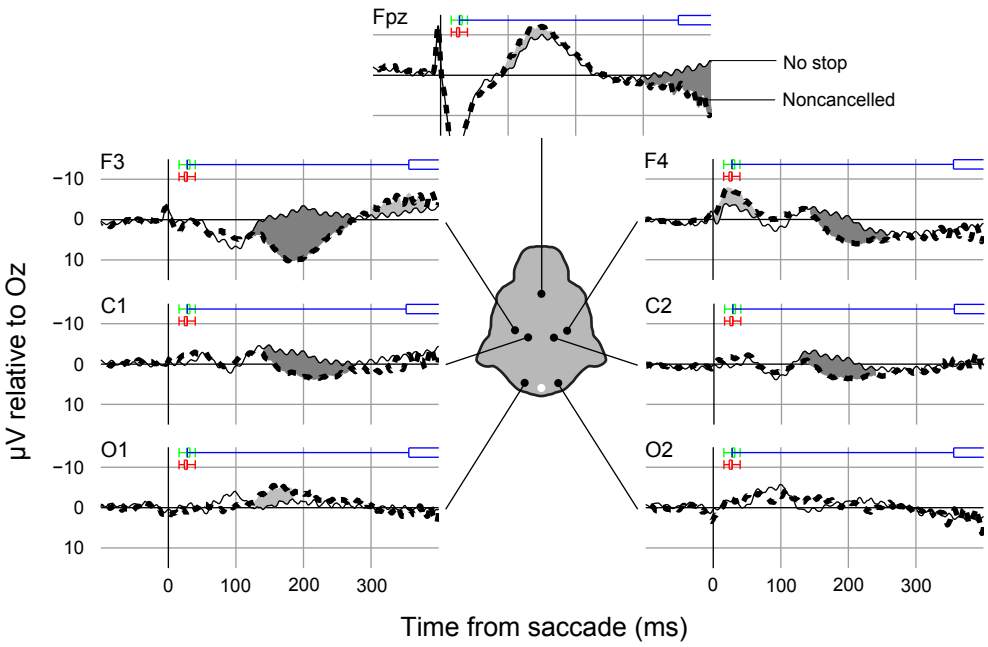

Figure 5.4: Error-related potentials from monkey F referenced to Oz. The axes plots the saccade-aligned ERPs for error noncancelled (1431 trials) and correct no stop saccades (7314 trials) across 15 sessions at each electrode location defined in the top left panel of Figure 2 (see also Table 1). The middle inset plots the stereotaxic location of the active electrodes (black), and the common reference electrode (white) on a diagram of a monkey head. Lines are drawn from selected electrodes to the corresponding axis. The single trial ERPs were truncated 50 ms before the subsequent task irrelevant saccade initiation. Blue box-whisker plots show latency of the subsequent task irrelevant saccades relative to response. Green and red box-whisker plots show the offset of the task saccade for no stop and noncancelled trials, respectively. Gray fill indicates periods of significant difference between correct and erroneous responses; dark gray indicates positivity, light gray indicates negativity (see Methods).

saccade contaminating the signal at frontal electrode locations. In order to address this possible confound, we recorded ERPs while referencing to the ears or mastoids.

Figure 5.5 plots comparisons of the saccade-aligned ERPs from monkey F on noncancelled trials and no stop signal trials collapsed across targets and referenced to the left ear (see Table 5.1). In this and all subsequent figures the conventions are the same as in Figure 5.4. Note that the data in the preceding figure and this one were

acquired under approximately the same behavioral conditions and reference, with the only differences being the number of surface electrodes implanted and the fact that monkey F had a midline recording well with a craniotomy. Significant positive polarization differences evolved at frontal electrodes, F3, F4, and the epidural electrode in the recording well (FpFz) $\sim$ 100 ms after saccade initiation. The significant positive polarization difference at electrodes F3-4 were followed by a significant negative polarization difference which occurred at $\sim$ 300 ms. The negative polarization at Fpz was followed by a positive polarization which occurred at $\sim$ 300 ms. There were also significant positive polarization differences at C1, C2 and Fpz occurring $\sim$ 300 ms after saccade initiation. Significant negative polarization differences were observed at all 3 occipital electrode locations and occurred $\sim$ 100 ms after the saccade initiation.

The original electrode configuration of monkey F was identical to that used in Woodman et al. (2007) with the majority of the electrodes implanted posterior to the central sulcus and thus ill-suited to measure potentials arising from frontomedial generators. We therefore subsequently repositioned electrodes by removing Fpz, C1, C2, F3, and F4 and implanting electrodes at FpFz, F1, and F2 (Figure 5.2B). Figure 5.6 plots comparisons of the saccade-aligned ERPs from monkey F on noncancelled trials and no stop signal trials collapsed across targets and referenced to the left ear for this new configuration of surface electrodes (see Table 5.1). Significant positive polarization differences evolved at all 3 frontal electrodes $\sim$ 100 ms after saccade initiation. At F1 and F2, these positive polarization differences were followed by significant negative polarizations evolving $\sim$ 150 ms after saccade initiation. At the occipital surface electrodes, O1 and O2, significant negative polarizations evolving

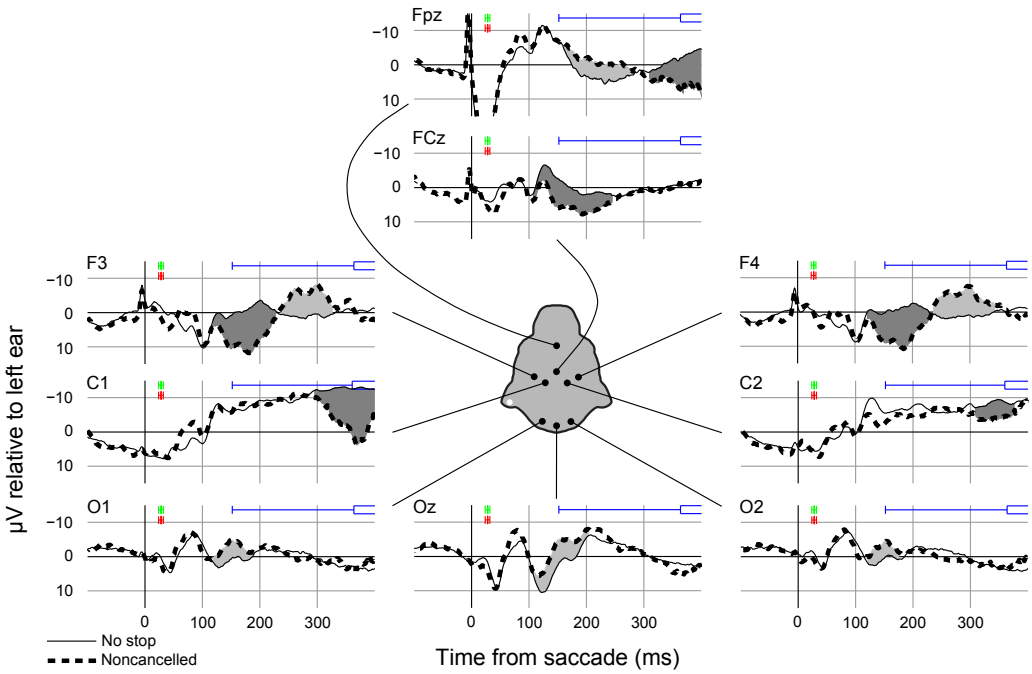

Figure 5.5: Error-related potentials from monkey F referenced to left ear. The axes plot the task saccade-aligned ERPs for error noncancelled (724 trials) and correct no stop saccades (234 trials) across 2 sessions at each electrode location defined in the top left panel of Figure 2 referenced to the left ear (see also Table 1). The conventions are the same as in Figure 4.

at $\sim$ 100 ms were followed by significant positive polarizations. Figure 5.6 plots data collected under the same behavioral conditions as previously reported from this laboratory (Emeric et al., 2008; Ito et al., 2003; Stuphorn et al., 2000). Note also that the data in Figure 5.6 and Figure 5.7 were acquired under approximately the same behavioral conditions and reference, with the only differences being the number of surface electrodes implanted and the fact that monkey F had a midline recording well with a craniotomy. Figure 5.7 plots comparisons of the saccade-aligned ERPs from monkey Y on noncancelled trials and no stop signal trials collapsed across targets and referenced to the left ear for selected electrodes (see Table 5.2). Significant positive polarization differences evolved at all the frontal electrodes - except FCz, Cz, and Fpz - $\sim$ 300 ms after saccade initiation. At electrodes FCz and Cz, significant positive polarization differences occurred at $\sim$ 150 ms. At electrode Fpz, the polarization difference was negative and occurred at $\sim$ 185 ms. Significant negative polarization differences were observed at parietal and occipital electrode locations except P3 and P4. At POz, O1, O2, and Oz, these polarizations occurred 90-140 ms after the saccade initiation. At Pz, the polarization occurred at $\sim$ 300 ms after the saccade initiation. At P4,there was a significant polarization at 315 ms following the saccade initiation.

The conditions under which the data in the preceeding plots were acquired are optimal for single units and LFPs acquired using high impedance depth electrodes but suboptimal for ERPs. For example, single units and LFPs in ACC were modulated following error noncancelled saccades but weakly modulated by visual stimuli such as the stop signal (Emeric et al., 2008; Ito et al., 2003). On the other hand, the feedback stimuli (e.g., auditory tones) may evoke ERPs which propagate to other

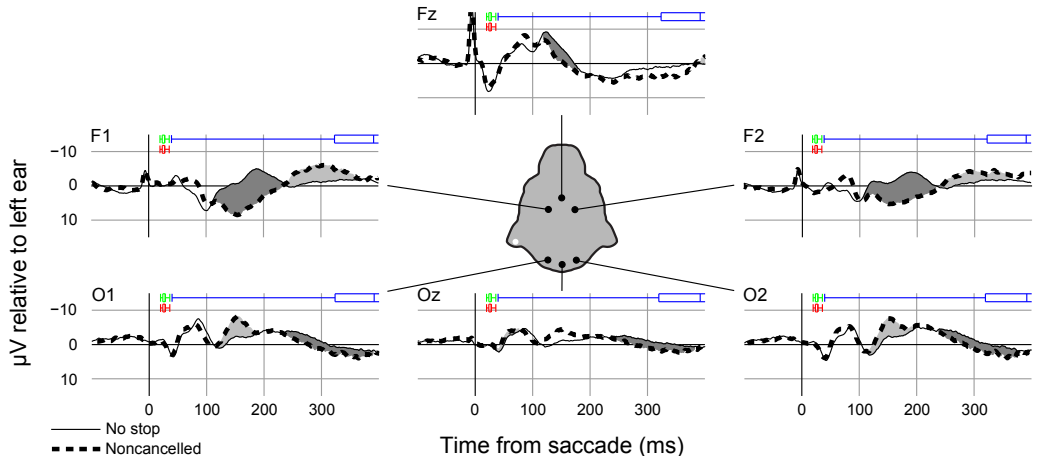

Figure 5.6: Error related potentials from monkey F's second electrode configuration referenced to left ear. The axes plot the task saccade-aligned ERPs for error noncancelled (1365 trials) and correct no stop saccades (2456 trials) across 2 sessions at each electrode location defined in the top right panel of Figure 2 referenced to left ear (see Table 1). The conventions are the same as in Figure 4.

surface electrodes and constructively or destructively interfere with the putative error monitoring potentials. To account for this confound, the data in the following plots were acquired during a version of the the stop signal task where the feedback stimuli were withheld (see Table 5.1). Figure 5.8 plots comparisons of the saccade-aligned ERPs from monkey F on noncancelled trials and no stop trials collapsed across targets and referenced to linked ears. Similar to Figure 5.7, a significant positive polarity evolves at electrodes F1 and F2 at $\sim$ 120 ms after saccade initiation. The saccade-aligned ERPs at Fz for error noncancelled and correct no stop trials were strongly but equally modulated so no significant polarity was observed at that electrode. A significant positive polarization evolved at electrode Oz that was simultaneous with the saccade onset. No other significant polarization evolved at the occipital electrodes.

Figure 5.9 plots comparisons of the saccade-aligned ERPs from monkey Y on noncancelled trials and no stop signal trials collapsed across targets and referenced to

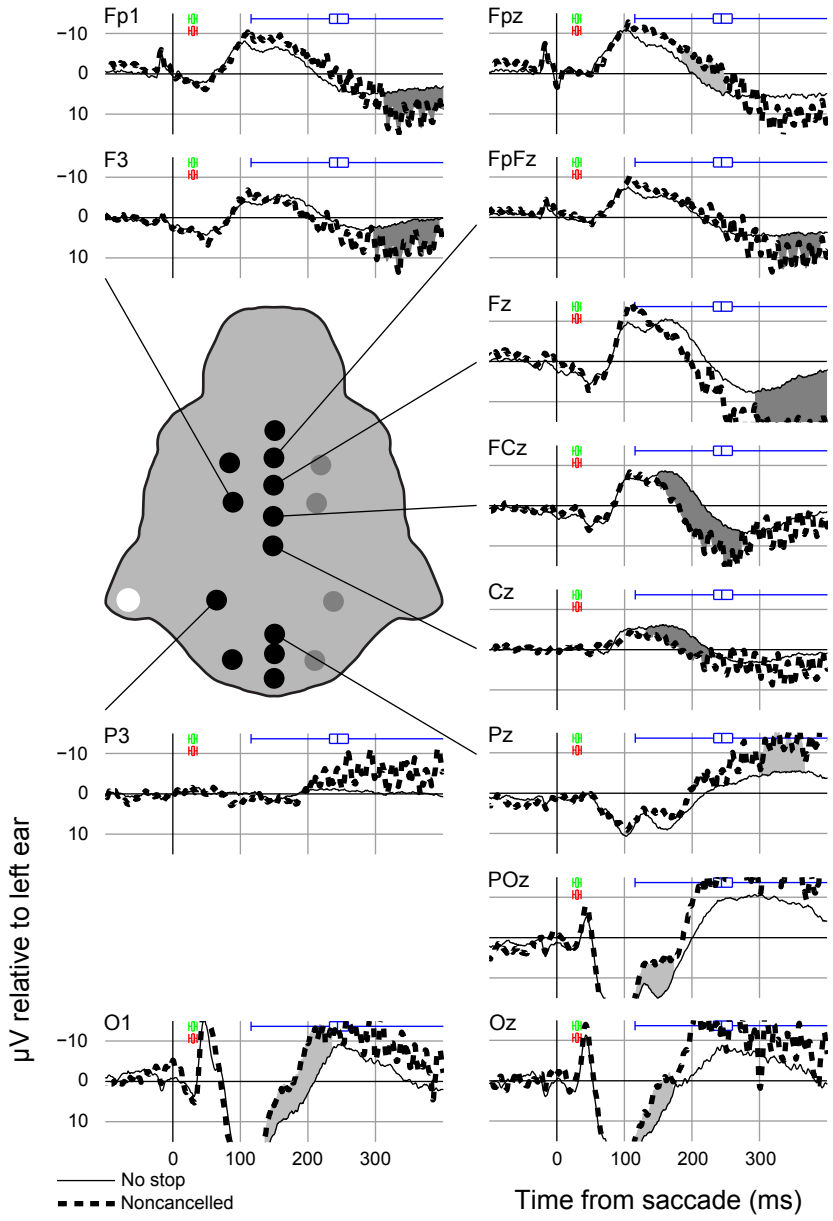

Figure 5.7: Error-related potentials from monkey Y referenced to the left ear. The axes plot the task saccade-aligned ERPs for noncancelled (112 trials) and correct no stop saccades (508 trials) from a single session at active electrode locations (black dots on the diagram of a monkey head) defined in Figure 2 referenced to the left ear (white dot; see Table 2). The conventions are the same as in Figure 4.

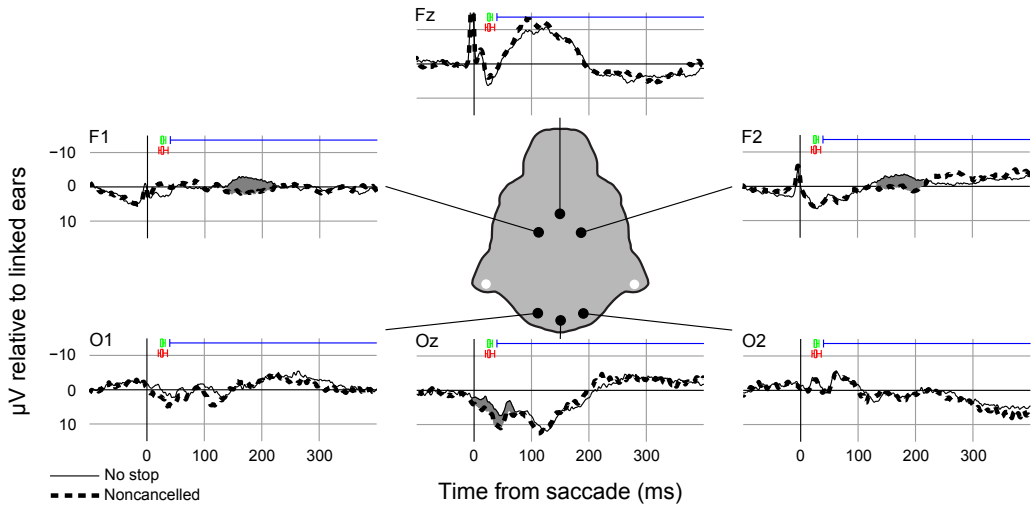

Figure 5.8: Error-related potentials from monkey F's second electrode configuration referenced to linked ears. The axes plot the task saccade-aligned ERPs for noncancelled (673 trials) and correct no stop saccades (1234 trials) across 5 sessions at each electrode location defined in Figure 2 referenced to linked ears (see Table 1). The conventions are the same as in Figure 4.

the left ear (see Table 5.2). Significant positive polarization differences evolved at all the frontal electrodes - except FCz, Cz, and Fpz - $\sim$ 300 ms after saccade initiation. At electrodes FCz and Cz, significant positive polarization differences occurred at $\sim$ 150 ms. At electrode Fpz, the polarization difference was positive and occurred at $\sim$ 150 ms. Significant negative polarization differences were observed at parietal and occipital electrode locations except P3 and P4. At POz, O1, O2, and Oz, these polarizations occurred 90-140 ms after the saccade initiation. At Pz, the polarization occurred at $\sim$ 300 ms after the saccade initiation. At P4,there was a significant polarization at $\sim$ 315 ms following the saccade initiation. The right inset of Figure 5.9 plots a topographic map of the mean voltage difference (error noncancelled ERP minus correct no stop ERP) in the 100-200 ms after the response, co-registered and projected onto the MRI reconstruction of Y's brain. In this time interval, we observe

that the significant positive potential difference at the frontal electrodes is largest in amplitude at the midline electrodes FCz and Cz. Also in this interval, the significant potential difference at the occipital and parietal electrodes is largest in amplitude at O1 and O2 and distributed laterally.

5.5 Discussion

We observed saccade and error-related ERPs in macaque monkeys performing a saccade stop signal task. Consistent with human error-related potentials, the error-related potentials reported herin were consistently distributed frontocentrally.

These results are part of a research program that is bridging human electrophysiology and monkey neurophysiology (Cohen et al., 2009; Emeric et al., 2008; Woodman et al., 2007). Several reports have described ERPs from human subjects performing stop signal tasks requiring manual responses (Bekker et al., 2005c; De Jong et al., 1995, 1990; Dimoska et al., 2006; Kok et al., 2004; Naito and Matsumura, 1994b; Naito et al., 1995; Pliszka et al., 2000; Ramautar et al., 2004, 2006b,a; Stahl and Gibbons, 2007; van Boxtel et al., 2001). While these studies generally focus on N2 and P3 components on stop signal and no stop signal trials, very few have examined response aligned ERPs during the stop signal task (Endrass et al., 2005; Liotti et al., 2005; Ramautar et al., 2004, 2006b,a) and only Endrass et al. (2005) has examined the ERN during an oculomotor version of the stop signal task. The results presented herein provide a evidence of a monkey homologue of the ERN and highlights the need for further investigation coordinated across species, task conditions, and effectors.

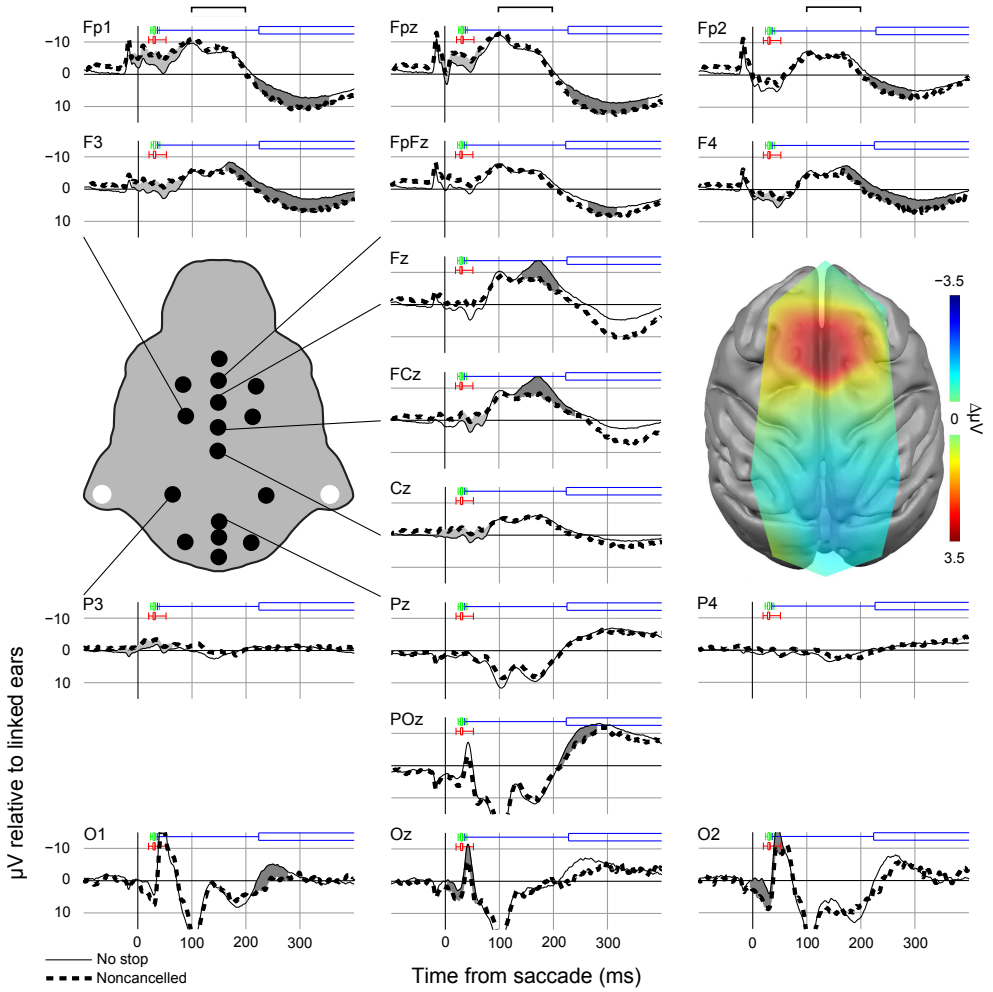

Figure 5.9: Distribution of error related potentials over the head for monkey Y referenced to the linked ears. The axes plot the task saccade-aligned ERPs error noncancelled (672 trials) and correct no stop saccades (3219 trials) across 5 sessions at each electrode location defined in Figure 2 referenced to the linked ears (white dots; see Table 2). Left inset, inset plots the active electrodes (black), and the common reference electrode is shown in white on a diagram of a monkey head. Right inset plots a topographic map of mean voltage difference (error minus correct) in the 100 ms time interval starting 100 ms after response co-registered and projected onto the same MRI reconstruction. The conventions are the same as in Figure 4.

5.5.1 Saccade related potentials: spike potential and λ-wave

The corneoretinal potential is generated by a concave sheet of electrical dipoles that can be approximated by a single equivalent dipole with its positive pole directed toward the cornea and located near the center of each eye (Lins et al., 1993b). Changes in the orientation of the corneoretinal potential during eye movements like saccades produce polarization that propagates onto surface EEG recordings. During conjugate eye movements, the regions of the scalp or face toward which the eyes turn become more positive and the regions away from which the eyes turn become more negative (see Figure 3; Geddes and Baker 1989; Lins et al. 1993a; Nativ et al. 1990; Weinstein et al. 1991).

Two distinct saccade related potentials were observed in this study. Saccades were preceded by the spike potential (Figure 5.3) which is thought to originate in the extraocular muscles through summation of EMG spikes during the rapid recruitment of motor units at saccade initiation (Moster and Goldberg 1990; Sparks 2002; but see Dimigen et al. 2009; Nativ et al. 1990; Parks and Corballis 2008). Consistent with these observations and that of Sander et al. (2010), we observed a monkey homologue of the spike potential that was negative and largest at the frontal electrode sites and whose polarity was inverted and smallest at occipital sites (Balaban and Weinstein, 1985; Brooks-Eidelberg and Adler, 1992; Moster and Goldberg, 1990; Thickbroom and Mastaglia, 1986).

In the interval after saccade termination, we observed the lambda potential (λ-wave) which is believed to be elicited by the afferent inflow beginning at fixation

following the visual suppression occurs during saccades (Dimigen et al., 2009; Kazai and Yagi, 2003; Thickbroom et al., 1991; Volkmann, 1986). Unlike the presaccadic spike potential, λ-wave amplitude does not scale with saccade amplitude (Dimigen et al., 2009). While the spike potential is considered to be of myogenic origin, the λ-wave considered a visual potential because is modulated by stimulus properties (Armington et al., 1967; Kazai and Yagi, 1999, 2003) and its dipole source has been localized in striate cortex (Kazai and Yagi, 2003). Identifying these ERPs in the nonhuman primate that are consistent in timing and polarity with human ERPs validates the technique used to acquire the ERPs and justifies the subsequent analyses.

5.5.2 Nonhuman primate homologue of the ERN

Saccade-aligned ERPs consistently exhibit greater positive polarization (error non-cancelled minus correct no stop) at electrodes Fz and FCz in the 100-200 ms after saccade onset across referencing and behavioral conditions (Figures 5.4-5.9). Electrophysiological studies have led to the current view that electrical potentials recorded at the scalp are the result of summed cortical LFPs, which are generated by the synchronous synaptic activity of populations of neurons. Consistent with this, previous reports from this laboratory have described error-related LFPs recorded from ACC and supplementary eye field (SEF) of monkeys performing the saccade stop signal task as homologes of the ERN (Emeric et al., 2008, 2010). Altogether, the data support the interpretation that the polarization difference in this report is homologous to the ERN described in studies of human ERP. If this identification is correct, then it provides an opportunity to investigate the location of the dipole(s) producing this

potential difference.

It is important to distinguish the results from this study and those in recent report by Vezoli and Procyk (2009) (see also Godlove 2010). The EEG electrodes used in this study are separated from current sources in the brain by cerebrospinal fluid, the skull, and the scalp. Vezoli and Procyk (2009) acquired surface electrical potentials via trans-cranial electrodes that were touching the dura which is effectively electrocortigography (ECoG) and thus not subject to the spatial filtering imposed by the skull. The major artifacts that compromise EEG, such as those caused by blinks and saccades, are less prominent in ECoG recordings and are absent from depth recordings (Ball et al., 2009). Consistent with this, Vezoli and Procyk (2009) did not observe saccade-evoked components in feedback-aligned ECoG (area 24c) while we observed clear saccade-evoked components in the ERPs but not LFPs in ACC (Emeric et al., 2008) or SEF (Emeric et al., 2010). In other words, the ERPs reported here are of the same biophysical properties as the ERPs recorded from normal human subjects while the preceding report data of the same biophysical properties as ECoG and depth recordings in humans (Vezoli and Procyk, 2009; Emeric et al., 2008, 2010).

5.5.3 Saccade-related performance monitoring signals

Several reports have described ERPs and imaging data from human subjects performing the antisaccade task as it relates to performance monitoring (Belopolsky and Kramer, 2006; Endrass et al., 2007; Klein et al., 2007; Nieuwenhuis et al., 2001; Polli et al., 2005; Van 't Ent and Apkarian, 1999). The imaging studies report activation in the SEF and ACC which is greater for antisaccades versus prosaccades. In

the antisaccade task, errant prosaccades are followed by short latency corrective saccades ($\sim$ 100 ms) which occur in the same interval as the ERN (e.g., Endrass et al. 2007; Nieuwenhuis et al. 2001). Unless efforts are made to account for the activity evoked by these corrective saccades, the potentials and activations in this task that are interpreted as performance monitoring should be viewed with some skepticism (see Godlove 2010). In the current oculomotor stop signal task performance, only Endrass et al. (2005) and Curtis et al. (2005) examined human brain activity related to performance monitoring. Endrass et al. (2005) observed the ERN occurring 70-100 ms following error noncancelled saccades. Differences in reference electrode and data processing limit the direct comparisons that can be made between this study and that of Endrass et al. (2005). First, Endrass et al. (2005) referenced signals to Cz and did not directly compare saccade-aligned error noncancelled ERPs to correct no stop ERPs. They defined the ERN as the largest negative polarization in the 70-100 ms time interval after the error saccade while we define the ERN using a difference wave (error ERP minus correct ERP) and signals were referenced either to the ears or Oz. Second, eye movement artifacts were removed using the multiple source eye correction method (Berg and Scherg, 1994) which effectively removes artifacts evoked by the time-locked saccade. On the other hand, the topographic map of the response locked ERN reported by Endrass et al. (2005) is consistent with that reported in this study (but reversed in polarity). Curtis et al. (2005) observed activations in SEF and ACC that were greater for stop signal trials than no stop signal trials. The activation in SEF discriminated cancelled from noncancelled trials. We observed a frontocentral positive polarization difference that was consistent with a generator in the medial

frontal cortex.

5.5.4 Error-related signals in SEF, ACC and ERP

The results of this study can be directly compared to a previous reports of LFP signals in the ACC and SEF of monkeys performing the saccade stop signal task by Emeric et al. (2008, 2010). First, we observe the spike potential in the surface ERPs of the frontal electrodes. We observed no evidence of a spike potentials in the SEF or ACC LFPs. The SEF LFPs were more polarized in the interval preceding the saccade, than those in ACC. Second, the incidence of postsaccadic polarization is not different between SEF, ACC, and the ERPs in this report. However, the incidence and amplitude of error-related LFPs was greater in ACC than SEF with greater negative polarizations following error noncancelled saccades than correct no stop saccades while the ERPs exhibit greater negative polarizations following correct no stop saccades than error noncancelled saccades.

Why do the ERPs in this study exhibit polarization patterns opposite that reported for the human ERN while the LFPs in ACC and SEF exhibit a pattern consistent with the human ERN? Cole et al. (2009) have suggested cross-species anatomical differences between human and nonhuman primates which can explain the absence of response conflict-related single unit and LFP responses in monkey single unit studies. While we do not necessarily agree with this conclusion (Schall and Emeric, 2010), gross morphological differences across the two species may explain the difference in polarization reported herein. The negative side of the potential field associated with any cortical structure lies above the apical dendrites of the pyramidal cells. The

human ERN is a negativity with a frontal central distribution, the negative pole of the equivalent dipole must point in this direction, where the scalp activity reaches a maximum. This constraint implies that the cortical layer that generates the ERN must run parallel to the area of the scalp where the ERN is maximal. The only human cortical structures that are oriented parallel to the apex of the skull are the cingulate and paracingulate sulci (Paus et al., 1996b,a; Vogt et al., 1995). Holroyd et al. (2002) argues that, because of the orientation of the dipole, the ERN must be generated within the ventral bank of the sulcus (area 24c), where the apical dendrites of the pyramidal cells point toward the scalp. In the monkey, only the cingulate is oriented parallel to the apex of the skull. However, in the monkey, the supplementary motor cortex extends two-thirds of the way down the dorsal bank of the cingulate sulcus. Area 24c wraps around the fundus of the sulcus and occupies most if not all of the ventral bank (Luppino et al., 1991; Matelli et al., 1985, 1991). While the orientation of this structure relative to the scalp is suggests that a frontocentral negativity should be observed in the monkey, Ito et al. (2003) and Emeric et al. (2008) observed single unit and LFPs with error-related modulation only in the dorsal bank of the cingulate sulcus. Emeric et al. (2008) reported larger amplitude negative polarizations following errors compared to correct saccades in area 24c. These LFPs were referenced to the dura, which means that the positive end of the dipole generating these potentials is pointed in the dorsal direction, opposite that observed in humans.

5.5.5 Source localization

Although, the dipole source of the ERN and functional activation (e.g., Menon et al. 2001) has been localized to the ACC, (e.g., Dehaene et al. 1994; Miltner et al. 1997; van Veen and Carter 2002), other investigations have implicated the dorsal medial frontal cortex including the pre-supplementary (pre-SMA) and supplementary motor areas (SMA) (e.g., Miltner et al. 1997. Functional imaging in humans has localized error-related activation in both the ACC and supplementary motor area as well as a number of other structures including the lateral prefrontal cortex, orbitofrontal cortex, and the striatum (e.g., Menon et al. 2001. Errors activate a network of regions including the ACC, pre-SMA, bilateral insula, thalamus and right inferior parietal lobule (reviewed by Hester et al. 2004). In addition to the cingulate cortex, intracerebral recordings in human patients have identified ERN-like potentials in the amygdala, hippocampus, parahippocampal gyrus, mesiotemporal region, lateral temporal region, orbitofrontal cortex, and dorsolateral prefrontal cortex (Brázdil et al., 2002b). Evidence from functional imaging has resulted in the same conflicting results regarding the neural substrate of the error-related negativity (reviewed by Hester et al. 2004).

The role of ACC in performance monitoring has been further supported by single unit and intracranial LFPs recordings in the ACC revealing increased activity after errors, reduced rewards, and the absence of expected rewards (Amiez et al., 2005; Emeric et al., 2008; Ito et al., 2003; Quilodran et al., 2008; Sallet et al., 2007; Vezoli and Procyk, 2009). Similar results have been observed in human anterior cingulate

neurons (Davis et al., 2005; Williams et al., 2004). Despite the aforementioned parallels between the human and nonhuman primate performance monitoring literature, the homology of the underlying neural substrate has been called into question because of contradictory results (e.g., Botvinick et al. 2004; Cole et al. 2009). A solution to this question, requires various techniques (i.e., single unit, LFPs, and ERPs) applied in an investigation of the same species. Establishing the existence of a performance monitoring ERP component in nonhuman primates indexing cognitive processes is an important first step towards resolving this question (e.g., Arthur and Starr 1984; Glover et al. 1991; Javitt et al. 1992; Paller et al. 1992; Woodman et al. 2007).

Conclusion

This study provides evidence of an homologue of the ERN in the ERPs of monkeys performing a saccade stop signal task. Electrophysiological studies have led to the current view that electrical potentials recorded at the scalp are the result of summed cortical LFPs, which are generated by the synchronous synaptic activity of populations of neurons. The coincidence of single unit activity in the ACC, error-related local field potentials, and error monitoring ERPs of identical biophysical properties as those acquired from humans provides a bridge between the human ERN literature and the monkey neurophysiology literature. These findings provide an avenue for more closely examining the neural events that give rise to human ERPs.

Acknowledgments

We thank Mary Feurtado and Troy Apple for skilled help with animal care and David Godlove and Courtney Segovis for brain MRI reconstructions. We also thank Stefan Everling for helpful discussion. This work was supported by National Institutes of Health Grants F32-EY017765, R01-MH55806, P30-EY08126, and P30-HD015052 and by Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience.

CHAPTER VI

CONCLUSION

> 'I had,' said he, 'come to an entirely erroneous conclusion which shows, my dear Watson, how dangerous it always is to reason from insufficient data.'
>
> — Sherlock Holmes - in Doyle (1981)

The studies contained in this thesis provide behavioral evidence of executive control and homologues of the ERN in the LFPs and ERPs of monkeys performing a saccade countermanding task. These findings provide an avenue for more closely examining the neural events that give rise to human ERPs.

6.1 Sequential dependencies during the stop signal task

Chapter II presented behavioral evidence of executive control in the form of response time adjustments and the probability of responding from humans and macaque monkeys in a saccade countermanding task that was influenced by stimulus and performance history. Based on a race between a GO and a STOP process with independent stochastic finish times, (Logan et al., 1984) demonstrated that the time needed to cancel a movement, SSRT, can be estimated from the distribution of response times when no stop signal is presented and the probability of responding given that a stop signal occurred, the inhibition function. The race model assumes that the finish times for the GO and STOP processes as a function of trial number are stationary stochastic processes with independence between trials. The race model of

countermanding performance makes no assumptions regarding the effect of stimulus and performance history on the outcome of subsequent trials. However, subjects display systematic changes in response time during performance of the stop signal task (Cabel et al., 2000; Emeric et al., 2007; Kornylo et al., 2003; Li et al., 2005; Özyurt et al., 2003; Rieger and Gauggel, 1999; Schachar et al., 2004; Verbruggen and Logan, 2008; Verbruggen et al., 2008).

Consistent with previous reports, Emeric et al. (2007) observed faster than average no stop signal response times following no stop signal trials and slower than average no stop signal response times following cancelled stop signal trials. Albeit inconsistently, these slowing and speeding of response times were accompanied by increased and decreased cancelled saccade probability, respectively. This is consistent with previous reports of post error slowing sans improved accuracy following errors (King et al., 2010; Rabbitt, 1977; Laming, 1979; Hajcak and Simons, 2008).

Paradoxically, Emeric et al. (2007) did not observe post error slowing. The authors interpreted this pattern of response time adjustments as resulting from the coactivation of mutually incompatible responses — shifting gaze versus holding gaze. Movement and fixation neurons are coactive during cancelled trials but only movement neurons are active on noncancelled trials (Hanes et al., 1998; Paré and Hanes, 2003). Botvinick et al. (2001) postulated that response conflict, the coactivation of mutually incompatible responses, is the signal used by the executive control system to trigger remedial action. Remedial action in this context is observed in the form of slower response times and improved accuracy following high conflict trials (reviewed by Botvinick et al. 2001; Botvinick 2007). Emeric et al. (2007) hypothesized that the

absence of post error slowing was the result of the absence of response conflict during noncancelled saccades.

Using the same dataset as Emeric et al. (2007), Nelson et al. (2010) has provided an alternative explanation. Nelson et al. (2010) showed that stop signal task response times are nonindependent and nonstationary. Nonindependent and nonstationary response times decrease the slope of inhibition functions and account for some of the systematic differences in response times following different types of trials. Nelson et al. (2010) showed that nonindependence and nonstationarity impact the measures of trial-to-trial response time adjustments described by Emeric et al. (2007). Specifically, Emeric et al. (2007) compared response times following different trials of interest (e.g., no stop response times following no stop versus cancelled versus noncancelled trials). Nelson et al. (2010) examined response times on trials both before and after a trial of interest to account for changes in response times due only to nonindependence and nonstationarity. Response times were relatively longer both before and after cancelled stop signal trials than before and after noncancelled trials, and response time was not specifically longer after cancelled than after noncancelled trials. With the exception of the absence of post error slowing, the trial history effects reported by Emeric et al. (2007) and Nelson et al. (2010), are in accord.

Taken all together, response time increases following stop signal trials and the probability of stopping is dependent on local fluctuations in nonindependent, nonstationary response times. Thus, the results indicate a general lengthening of response time following any stop signal trial. This posses a challenge for understanding the mechanisms whereby trial history affects performance (e.g., Botvinick et al. 2001;

Boucher et al. 2007a. In particular, the coactivation of movement and fixation units in the interactive race model of Boucher et al. (2007a) has been used as a measure of conflict and can account for the trial history effects reported by Emeric et al. (2007).

Alternative hypotheses regarding the mechanisms underlying response time adjustments include stimulusresponse priming and attentional capture (e.g., Nieuwenhuis et al. 2006; Notebaert et al. 2009). For example, Nieuwenhuis et al. (2006), response time slowing following high conflict trials may reflect associative stimulusresponse priming instead of conflict-driven adaptations in cognitive control. Consistent with this hypothesis, Rieger and Gauggel (1999) report greater response time adjustments in the stop signal task when the primary task (no stop trials) properties repeated (see also Verbruggen et al. 2005). Notebaert et al. (2009) propose that post-error slowing is caused by the relative infrequency of errors which causes attentional capture. This may also be a plausible account of post stop signal slowing because stop signal trials are the minority of trials and approximately half result in noncancelled errors. Further investigation is required for a parsimonious mechanism of these response time adjustments to be plausible.

6.2 Intracranial local field potentials recorded in the medial frontal cortex

Chapters III and IV describe intracranial local field potentials recorded in the ACC and SEF of macaque monkeys performing a saccade countermanding task. The results provide clear evidence that error- and feedback-related signals are carried by the local field potentials in the macaque medial frontal cortex. The results of these studies are measures of field potentials in the medial frontal cortex of monkeys performing a

saccade countermanding task which exhibit patterns of modulation consistent with accounts of the functional significance of the ERN. Such hypotheses ultimately require measurements of single units and field potentials that can be compared with the surface field potentials. The hypotheses regarding the functional significance of the ERN ultimately require measurements of single units and field potentials that can be compared with the surface field potentials. Characterizing intracranial homologues of the ERN is a necessary bridge.

Taken all together, the results of these studies suggest slightly different roles for SEF and ACC in the initiation and control of saccadic eye movements. First, the stimulus-aligned LFPs in SEF onset earlier and are clearly more polarized than the LFPs in ACC. In the interval preceding the saccade, the SEF LFPs were more polarized than the ACC LFPs and this polarization was frequently observed in the SEF but less often in the ACC. Neither SEF nor ACC LFPs produced signals sufficient to control gaze. The pattern of SEF LFP polarization was consistent with that predicted by the conflict monitoring hypothesis this was not observed in ACC. The incidence of postsaccadic polarization was not different between SEF and ACC. However, the incidence and amplitude of error-related potentials was greater in ACC than SEF. Finally, while Emeric et al. (2008) observed reinforcement-related LFPs in ACC, Emeric et al. (2010) report the absence of such modulation in the SEF LFPs. Taken all together, the results suggest that, despite sharing functional properties, the two areas participate in different aspects of motor behavior: the SEF integrates external stimuli while the ACC monitors internal states during motor planning.

Electrophysiological studies have led to the current view that electrical potentials

recorded at the scalp are the result of summed cortical LFPs, which are generated by the synchronous synaptic activity of populations of neurons. However, the event-related LFPs reported in this thesis differ from previous reports (e.g., Dias et al. 2006). Previous studies have used a linear electrode arrays to densely sample the intracranial field potential distribution and identify local dipoles (Schroeder et al., 1998). Chapters III and IV describe LFPs recorded at single contact electrodes referenced to the dura (∼3-8 mm away). These LFPs are the voltage difference between the scalp and the ACC or SEF. Due to superposition, potentials generated by local and remote sources and sinks add algebraically at any given point so interpreting field potentials entirely in terms of local generators is uncertain. Thus it is possible that the field potentials described in Chapter III in the dorsal bank of the ACC arose from dipoles in, for example, the ventral bank of the ACC or more dorsally in the SEF. The converse can be said for the SEF field potentials described in IV. Evidence against this concern, though, includes preliminary results we have obtained showing attenuated or absent error-related field potentials in the ventral bank of the ACC (Emeric et al., 2003) and that error-related potentials are less commonly observed in the SEF. Moreover, the magnitude of the grand average error-related potentials in ACC is an order of magnitude greater in ACC than SEF. Nevertheless, to resolve this localization problem most definitely, it will be necessary to record current source density across the medial frontal cortex, spanning the layers of the dorsal and ventral banks of the ACC and SEF (e.g., Dias et al. 2006). The coincidence of error-related single unit activity and local field potentials in the ACC and SEF and error monitoring ERPs of identical biophysical properties as those acquired from humans provides a bridge

between the human ERN literature and the monkey neurophysiology literature.

6.3 Event-related potentials measuring error detection and performance monitoring in nonhuman primates

Chapter V provides evidence of an error-related component similar to the ERN found in humans. During the stop signal task, the most prominent feature was a frontocentral positivity following unrewarded errors compared to rewarded correct trials. These findings establish a bridge between neurophysiological studies of performance monitoring in humans and non-human primates. Further work is required to determine the relationship of this potential to demands in performance monitoring.

6.4 Hypotheses of the functional significance of the ERN

The presence of surface and intracranial event-related field potentials similar to the ERN in monkeys provides leverage for rigorously testing models of the functional significance of the ERN using simultaneously acquired single units, intracranial LFPs, and surface ERP methods in nonhuman primates (e.g., Cole et al. 2009). Previous work in this lab has identified error-, reward-, and conflict-related single units in the medial frontal cortex of monkeys performing a saccade stop signal task (Ito et al., 2003; Stuphorn et al., 2000). The studies described in this thesis have established that event-related LFPs and surface potentials in nonhuman primates carry signals consistent with hypotheses of the functional significance of the ERN.

The most common signal observed in the event-related LFPs in ACC and SEF was greater negative polarization following error noncancelled saccades than correct

no stop saccades. This negative polarization was followed by positive polarization that was greater for correct no stop signal saccades than error noncancelled saccades. Significant polarization was not evoked by the stop signal on cancelled trials, therefore the polarization observed on noncancelled trials could not be attributed to the stop signal. The location, polarity, time course, and context by which these LFPs are evoked is consistent with the conditions under which the ERN is evoked. We therefore interpreted these LFPs as error related.

The ERN is observed in a variety of experimental conditions (reviewed by Taylor et al. 2007). For example, the ERN has been observed after partial errors (e.g., Coles et al. 1995). The only errors observed in the saccade stop signal task are noncancelled saccades. Saccades are ballistic in nature; therefore, partial errors cannot be examined in the stop signal task. Further work is required to examine the range of errors which may evoke these potentials (e.g., error saccades to distractors in a visual search task).

Motivated by previous computational models, Holroyd and Coles (2002) simulated and examined the behavior of the response locked and feedback ERN. They later extended this model to account for response times in speeded response time tasks (Holroyd et al., 2005). We also examined the ACC and SEF LFPs for evidence of reinforcement learning signals by comparing the LFPs aligned on the time of reinforcement during trials where earned reinforcement was delivered versus during trials where it was withheld. We observed a significant negative-going potential in 40% of the ACC sites. No such potentials were observed in the SEF. This is consistent with the reinforcement learning hypothesis prediction that the ERN is generated by the ACC (reviewed by Schultz 2002). Future work will examine if ACC and SEF LFPs

are modulated by manipulations such as those employed by (Holroyd and Coles 2002; Holroyd et al. 2005; e.g., manipulating the frequency of stop signal trials).

The conflict-monitoring hypothesis proposes that control is recruited based on the coactivation of mutually incompatible response processes (Botvinick et al., 2001, 2004). Physiological recordings of FEF/SC movement and fixation neurons has revealed that (1) gaze shifts are triggered when movement neuron activity reaches a constant threshold and the activity of fixation neurons decreases and (2) gaze shifts are cancelled when movement neurons activity does not reach the fixed threshold and fixation neurons become active before SSRT (Hanes and Schall, 1996; Hanes et al., 1998; Paré and Hanes, 2003; Brown et al., 2008). The coactivation of movement and fixation neurons increases on cancelled trials with the probability of a noncancelled saccade but not noncancelled trials. Stuphorn et al. (2000) observed a subpopulation of SEF neurons that were modulated after SSRT on cancelled but not noncancelled trials. This modulation was positively correlated with the probability of a noncancelled saccade. This pattern of activity was interpreted as being conflict-related activity Stuphorn et al. (2000). Ito et al. (2003) did not observe ACC neurons with conflict-related activity. Consistent with Ito et al. (2003), Chapter III reports an absence of conflict-related polarization in the ACC event-related LFPs. Chapter IV reports a pattern of SEF LFP polarization that is consistent with that predicted by the conflict monitoring hypothesis this was not observed in ACC.

The interpretation of conflict-related activity in SEF hinges on the coactivation of movement and fixation cells on cancelled trials but not noncancelled trials. In other words, response conflict is present on cancelled but not on noncancelled trials. The

absence of post-error slowing was interpreted as further support for the absence of conflict on noncancelled trials (Emeric et al., 2007). Boucher et al. (2007b) used the coactivation of movement and fixation units in the interactive race model and was able to replicate the behavioral result observed by (Emeric et al., 2007). The observation that response time increases following both cancelled and noncancelled stop signal trials calls into question the mechanisms by which these behavioral adjustments occur Nelson et al. (2010). It remains to be seen whetherresponse time adjustments observed in the stop signal task can be explained by the the response conflict hypothesis.

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