Testing animal models of human oculomotor control with neuroimaging

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Summary - We know more about the primate oculomotor system than any other motor system. From numerous studies that have measured electrical activity in single neurons, applied electrical microstimulation, characterized the behavioral sequelae of lesions, and mapped the afferent and efferent connections in oculomotor areas, exquisite animal models of human oculomotor control have evolved. In this chapter, I review studies that have begun to test these animal models in humans using neuroimaging techniques. I hope to highlight the importance of this form of translational research by describing several successes involving our understanding of the roles of the frontal and parietal cortex in saccade control. Moreover, I will discuss several problematic methodological issues that have proven challenging to our efforts of translation.

The primate oculomotor network - The superior colliculus (SC) is a phylogenetically ancient midbrain structure whose neural activity is synonymous with the conversion of sensory signals to commands used to control gaze (D. L. Robinson & McClurkin, 1989; Sparks & Hartwich-Young, 1989)(see also chapter by White and Munoz in the current volume). Indeed, there are both visual and motor topographic maps within the SC's laminated intermediate and superficial layers, respectively. The SC is thought to reflect a convergence point where a variety of afferent cortical and subcortical signals are weighed, averaged, and compared to produce saccade commands (Krauzlis, Liston, & Carello, 2004; Moschovakis, 1996; Munoz & Fecteau, 2002). The SC is particularly well positioned anatomically in the primate brain to integrate such signals (May, 2006). Importantly, in addition to visual signals from striate cortex that target the SC, a number of other cortical areas are known to influence neural activity in the SC. The frontal cortex contains over four distinct areas whose monosynaptic connections with the SC are thought to influence gaze programming. David Ferrier first reported that electrical stimulation of the monkey dorsal frontal cortex evoked contraversive eye movements (Ferrier, 1886). A dorsolateral portion of the large region he described has become known as the frontal eye field (FEF). With microstimulation, the FEF has been more precisely localized to the anterior bank of the arcuate sulcus in Brodmann's area 8 (Bruce, Friedman, Kraus, & Stanton, 2004; Bruce & Goldberg, 1985; Bruce, Goldberg, Bushnell, & Stanton, 1985; D. A. Robinson & Fuchs, 1969; Schall, 1991), where saccades can be elicited with very low current thresholds (< 50 μA). However, the boundaries of the functionally defined monkey FEF remain unclear and may extend into Brodmann's area 6 and Walker's area 45 (Petrides & Pandya, 2002; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000). The FEF contains an organized map of mostly contralateral visual space defined in eye-centered coordinates (Bruce, et al., 1985; Sommer & Wurtz, 2000). A rough progression of cells that code for large to short amplitude saccades can be found as one moves along the long axis of the FEF from dorsomedial to dorsolateral arcuate sulcus. Indeed, the dorsal and ventral visual streams in extrastriate cortex send topographical projections to the the dosomedial and dorsolateral FEF, respectively, that are thought to be used for orienting to extrafoveal space and visually exploring objects near the fovea (Schall, Morel, King, & Bullier, 1995). Several types of FEF neurons have been described, including ones that respond prior to and during the generation of saccades (i.e., saccade or motor neurons), ones that pause during saccades but are active during fixation (i.e., fixation neurons), and ones that respond when a behaviorally relevant stimulus is in its receptive field (i.e., visual neurons) (Bruce, et al., 2004; Schall, 2002). However, the most common FEF neuron responds to both visual stimulation and motor plans (i.e., visuomotor neurons). Several cortical areas adjacent to the FEF in the premotor and prefrontal cortex often show saccade related neural activity (e.g., (Fujii, Mushiake, & Tanji, 1998; S. Funahashi, C. J. Bruce, & P. S. Goldman-Rakic, 1989a; Schlag & Schlag-Rey, 1987). These areas, although are not involved in generating saccade commands, are thought to contribute to gaze control. For example, neural activity in the lateral prefrontal cortex (PFC), in and around the principal sulcus, is related to cognitive factors that affect gaze (see also chapter by Johnston and Everling in the current volume). For example, neurons in PFC fire persistently during the maintenance of endogenous saccade plans (Funahashi, et al., 1989a; Funahashi, Bruce, & Goldman-Rakic, 1991). The

contributions of neurons in the supplementary eye field (SEF) and dorsal anterior cingulate cortex (dACC) are less well understood, but in general are thought to involve higher cognitive processes that influence gaze. For example, neurons in these dorsomedial frontal areas track factors upon which eye movements are conditional (Olson & Gettner, 2002; Roesch & Olson, 2003), encode the learning of arbitrary visuomotor transformations (Chen & Wise, 1995a, 1995b, 1996; Parton, et al., 2007) and sequences of eye movements (Isoda & Tanji, 2002, 2003; X. Lu, Matsuzawa, & Hikosaka, 2002), and monitor performance or decision variables associated with eye movements (Ito, Stuphorn, Brown, & Schall, 2003; Schall, Stuphorn, & Brown, 2002; Stuphorn, Taylor, & Schall, 2000b). In the parietal cortex, the lateral intraparietal (LIP) area is known to play an important role in oculomotor behavior (Gottlieb, Kusunoki, & Goldberg, 1998; Mazzoni, Bracewell, Barash, & Andersen, 1996) (see also chapter by Paré and Dorris in the current volume) and is sometimes referred to by a functional label, the "parietal eye field." In many respects, LIP mimics the functions that have been ascribed to the FEF because almost identical patterns of neural activity have been found in LIP and FEF neurons during a wide variety of oculomotor behaviors. One main difference is that saccades are not reliably evoked with microstimulation of LIP neurons until current levels are quite high (< 120 μA) (Mushiake, Fujii, & Tanji, 1999) and therefore are not defined with stimulation. Recent evidence suggests that LIP neurons represent not only the sensory evidence favoring an eye movement, but the expected values of potential eye movements (Coe, Tomihara, Matsuzawa, & Hikosaka, 2002; Curtis & Lee, 2010; Glimcher, 2003; Glimcher & Rustichini, 2004; Platt & Glimcher, 1999; Seo, Barraclough, & Lee, 2009). In summary, a variety of cortical areas provide inputs to the SC allowing our gaze to be controlled by visual, motor, cognitive, and motivational factors.

Translating monkey electrophysiology to human neuroimaging - Findings from monkey electrophysiological studies of the oculomotor system have been used to develop rich models of oculomotion and cognition. These models have guided the hypotheses and interpretations of data in neuroimaging research. In return, neuroimaging research has the potential to translate these findings from monkey to human. The importance of this step should not be underestimated. Until researchers test candidate animal models of human oculomotor control in humans, the efforts and contributions to neuroscience that the animal researchers are making are undermined. Translation, however, is not easy for several reasons, most notably the differences in the methodologies available and inherent differences in the species themselves. Below I describe both the successes researchers have made as well as the problems that challenge the field.

Localizing oculomotor areas - If we are to translate and test animal models in humans, as a starting point we must first confirm that we can reliably localize homologous regions across the species. As mentioned above, monkey areas FEF and LIP can be localized using electrical microstimulation and a characteristic pattern of neural firing during memory-guided saccade tasks, respectively. Recently, fMRI studies of monkeys performing saccade tasks provided strong evidence that FEF and LIP defined by fMRI corresponds very well to electrophysiological methods (Baker, Patel, Corbetta, &

Snyder, 2006; Ford, Gati, Menon, & Everling, 2009; Koyama, et al., 2004) (See Figure 1A/B). Saccade production evoked BOLD activation along the monkey arcuate sulcus in FEF and intraparietal sulcus in area LIP. This is important because it shows, at least within species, that localizing oculomotor structures using BOLD imaging agrees with electrophysiological methods.

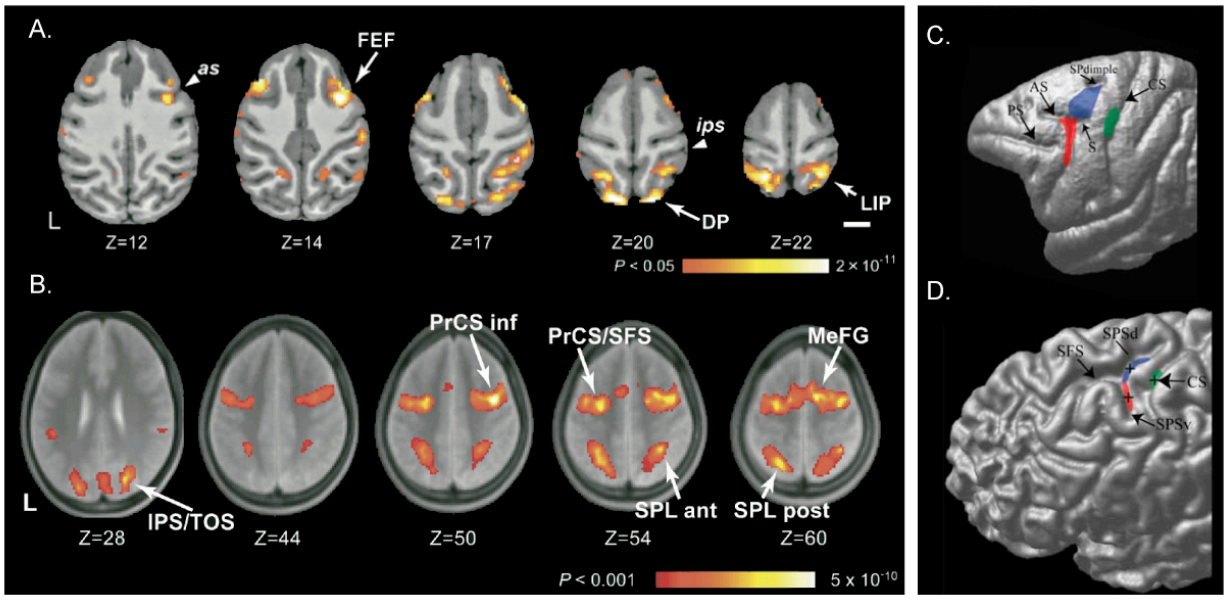

Figure 1. The homology of oculomotor areas in monkey and human. BOLD responses evoked by saccades in (A.) monkeys and (B.) humans using fMRI (Koyama et al., 2004) show promising homology. The monkey areas FEF and LIP appear to have putative homologies in human dorsal precentral and intraparietal sulci, respectively. Note that in humans, activation can be seen in the superior and inferior branches of the precentral sulcus making it difficult to localize the FEF in humans. C. These two areas may correspond to the monkey dorsal premotor cortex (blue) and FEF (red). D. In humans, saccades evoke activation all along the precentral sulcus. However, the portion of the precentral sulcus that is dorsal to the junction of the superior frontal sulcus (blue) shows relatively greater hand movement related activity, while the portion ventral to the junction (red) shows relatively greater eye movement related activity (Amiez et al., 2006).

What homologies might we expect in humans? Although the SC is the most studied node in the oculomotor network in non-human primates, it has not been well studied in humans using brain imaging because of its small size (i.e., not much bigger than a few standard size MRI voxels) and the artifacts arising from pulsating vasculature near the SC. Instead, the most intensive work attempting to find human homologs of oculomotor areas have focused on FEF and LIP. Intraoperative electrical stimulation of the human dorsal frontal cortex evokes contraversive eye movements (Blanke & Seeck, 2003; Blanke, et al., 2000; Lobel, et al., 2001; Penfield & Boldrey, 1937). Such invasive procedures, however, are not practical for most investigations into the functions of the FEF. Transcranial Magnetic Stimulation (TMS) does not evoke eye movements (Zangemeister, Canavan, & Hoemberg, 1995) like electrical microstimulation does. Therefore, functional imaging will be key to localizing and studying the human oculomotor network. Early positron emission tomography (PET) studies localized the putative human homolog of the monkey FEF in the precentral sulcus (Paus, 1996; Sweeney, et al., 1996). This was surprising given that it places the FEF in agranular

cortex (Rosano, et al., 2002; Rosano, Sweeney, Melchitzky, & Lewis, 2003), within Brodmann's area 6, and far caudal than would be predicted by the location of the monkey FEF. Subsequent fMRI studies that have imaged saccade production have supported the localization of the FEF in the dorsal precentral sulcus near its junction with the superior frontal sulcus (Brown, et al., 2004; Connolly, Goodale, Desouza, Menon, & Vilis, 2000; Cornelissen, et al., 2002; Curtis, 2006; DeSouza, Menon, & Everling, 2003; Grosbras, et al., 2001; Heide, et al., 2001; Kimmig, et al., 2001; Luna, et al., 1998; Petit, Clark, Ingeholm, & Haxby, 1997; Postle, Berger, Taich, & D'Esposito, 2000; Rosano, et al., 2002).

Animal researchers have benefited tremendously from having a reliable method to define the FEF (< 50ua stimulation evokes saccade). With similar goals in mind, human fMRI researchers have used "saccade localizers" to identify the same oculomotor areas across subjects and across labs. In particular, saccade localizers have been used to identify the putative human FEF. This typically involves scanning subjects as they make visually guided saccades interleaved with central fixation. Compared to central fixation, saccades do indeed evoke activation in the superior portion of the precentral sulcus, the putative human homolog of the monkey FEF (See Figure 1B).

However, several other areas in the precentral, superior frontal, and inferior frontal sulci also activate during saccade production making it difficult to determine which of these are the homologs of monkey FEF. Moreover, defining the boundaries of the candidate FEF is an unreliable procedure because it depends on the statistical threshold used. Too low a threshold, even if statistically significant, and the entire precentral sulcus is often active. Too high a threshold, and the only statistically significant voxels that survive might be ones that are not in the superior precentral sulcus. The consequence is that researchers often use their judgement to decide which voxels to include in their FEF region-of-interest (ROI). Many studies label any activation in the precentral sulcus as FEF, regardless of its location. Additionally, other behaviors besides saccade production are invoked during performance of saccade localizer tasks, including visual, attentional, and motivational factors that may evoke spurious activations. For example, visual cortex is often activated by saccade localizer tasks. Despite their widespread use, the lesson here is that typical saccade localizers do not identify saccade-specific areas. Nonetheless, a small number of putative FEF candidates can readily be defined with functional imaging such that one can compare the physiological responses of different portions in and around the precentral sulcus during tasks that require different sensory, motor, and cognitive processes. Here is a great example from Michael Petrides' lab. Amiez, Kostopoulos, Champod, and Petrides (Amiez, Kostopoulos, Champod, & Petrides, 2006) reported that both conditional eye and hand movements evoked BOLD responses in the superior precentral sulcus. However, greater responses to hand compared to eye were found in the segment of the precentral sulcus dorsal to the junction with the superior frontal sulcus. Conversely, greater responses to eye compared to hand were found in the segment of the superior precentral sulcus just ventral of the junction with the superior frontal sulcus. These findings appear to be homologous to the geometric relationship between the monkey FEF and dorsal premotor areas (Fig 1C/D). These results make two important points. First, they

suggest that researchers cannot assume that activation in the superior precentral sulcus is synonymous with FEF activation. Hand movements evoke activation strongly in the dorsal segment of the superior precentral sulcus and even in the ventral segment thought to be the FEF (Astafiev, et al., 2003; Connolly, Goodale, Cant, & Munoz, 2007; Levy, Schluppeck, Heeger, & Glimcher, 2007). Second, these putative functional areas are yoked to an anatomical fiducial, the junction with the superior frontal sulcus, which is variable in shape and folding across individuals. Therefore, group studies that simply normalize the anatomy of subjects in volume space without constraining the registration to align the junction of the superior and precentral sulci across subjects could lead to misregistration and Type II error.

An exercise in testing our assumptions for translation - The ability to localize homologous areas between humans and monkeys through non-invasive imaging techniques has been a major breakthrough. Nonetheless, before researchers can confidently begin to test and translate models between the species, we must ask how do we translate between electrophysiological methods and neuroimaging methods. For example, because researchers have shown that neurons in the monkey FEF increase in spike rate prior to the execution of saccades, one might predict that BOLD activity should increase prior to saccades in human FEF. However, as has been much discussed in the last 10 years, the relationship between spiking and BOLD remains controversial (Logothetis, 2002; Nir, et al., 2007). BOLD is an indirect measure of neural physiology. Local BOLD signal can be affected by the spiking of large pyramidal neurons, whose activity is largely thought to reflect the output of local computation, the spiking of small interneurons, whose activity is thought to reflect local computation, and a variety of metabolic processes in post-synaptic neurons, whose activity is thought to reflect incoming signals used in the local computations (Logothetis & Wandell, 2004). Several compelling lines of evidence suggest that BOLD is most strongly coupled with local field potentials (LFPs), which are strongly coupled with post-synaptic neural effects (Goense & Logothetis, 2008; Kayser, Kim, Ugurbil, Kim, & Konig, 2004; Kim & Ugurbil, 1997; Logothetis, 2002; Maier, et al., 2008; Masamoto, Vazquez, Wang, & Kim, 2008; Rauch, Rainer, Augath, Oeltermann, & Logothetis, 2008; Rauch, Rainer, & Logothetis, 2008). Frankly, this presents a problem for researchers trying to translate monkey electrophysiology studies that use spike rate as a dependent variable and human studies that use BOLD as a dependent variable. Fortunately, from a very practical standpoint much translational work can proceed even in the absence of complete parity in the methods. Spike rate and BOLD are significantly correlated (although not quite as strongly as with LFPs) (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), and spike rate and LFPs are highly correlated and these correlations will get stronger as one integrates over periods that match the timescale of BOLD (i.e., on the order of seconds). Therefore, electrophysiology data can be used by BOLD imaging studies to guide predictions.

Assuming, however, that BOLD is synonymous with spike rate is fallible and studies should build into their research checks on this assumption. Since this is one of the biggest challenges to human imaging researchers, I would like to illustrate how this can be done. First, let us assume we have identified the putative human FEF (see above).

Second, let us take a set of findings from electrophysiological monkey studies that we believe should no doubt exist in the human homolog of the FEF. In this exercise, we will consider recordings from monkey FEF during memory-guided saccade tasks. Here is what we know. In FEF neurons, persistent activity (i.e., tonically increased spike rate) (a) is observed during the memory delay (Bruce & Goldberg, 1985; Funahashi, et al., 1989a; Funahashi, Bruce, & Goldman-Rakic, 1993; Goldberg & Bruce, 1990; Lawrence, White, & Snyder, 2005; Segraves & Goldberg, 1987; Sommer & Wurtz, 2000, 2001; Takeda & Funahashi, 2002, 2004; Umeno & Goldberg, 2001), (b) is greater in neurons in the hemisphere contralateral to the memoranda (Bruce & Goldberg, 1985; Funahashi, et al., 1993; Goldberg & Bruce, 1990; Lawrence, et al., 2005; Sommer & Wurtz, 2000, 2001), (c) scales with the length of the memory delay (S. Funahashi, C.J. Bruce, & P.S. Goldman-Rakic, 1989b), and (d) correlates with performance accuracy (Funahashi, et al., 1989b). BOLD changes should show a similar pattern if researchers intend to base their interpretations on monkey electrophysiological data. Indeed, BOLD signal in the putative human FEF changes in ways that would be predicted from the spike data from monkey FEF. Several studies from different laboratories have shown that BOLD signal in the FEF persists above pretrial baseline throughout the memory delay (Brown, et al., 2004; Curtis, 2006; Curtis & D'Esposito, 2006; Curtis, Rao, & D'Esposito, 2004; Srimal & Curtis, 2008). Moreover, the persistent activity shows a contralateral bias, scales with the length of the delay, and correlates with performance accuracy (Figure 2). The electrophysiological data in the monkey and the BOLD data in the human converge in this case and strongly suggest that the FEF play an important role in the maintenance of saccade goals. The activity appears to be mnemonic in nature because it persists until the memory-guided saccade is made and its level of activity correlates with the fidelity of the later memory-guided saccade. Its activity provides the bridge across time that links the visually cued location and contingent delayed response. The neural mechanism of spatial working memory may be persistent activity in neurons that code for contralateral space or contraversive eye movements. Moreover, these results strongly suggest that BOLD data from humans can be predicted from spiking data from monkeys at least under these simple controlled circumstances. Notice, however, there are a few striking differences between the monkey spike data and the human BOLD data that are worth noting. The time-scales between the two are very different. Spikes can be recorded at a millisecond resolution, but hemodynamic responses are sluggish and take several seconds to resolve. Therefore, the experiments have to be designed very differently with more severe constraints on the BOLD designs where the resolution of sub-trial events (e.g., cue, delay, response epochs) necessitate both temporal spacing and jittering of spacing (e.g., in the example, the cue and response was spaced apart from one another by long and variable length delays). One must always be wary that these modifications may change the nature of the task and behavioral data can be used to test this possibility. More importantly, notice that the contralateral BOLD responses are only slightly (i.e., ~10%) greater than the ipsilateral responses. From the spike data, we would predict that this difference would be much greater. The probable reason is that BOLD responses are driven by both spiking, that is highly contralateralized, and post-synaptic activity, that is not. Specifically, inhibitory post-synaptic potentials may cause increased BOLD responses in the ipsilateral FEF. Indeed, transcollosal homotopic projections from the contralateral to the ipsilateral FEF

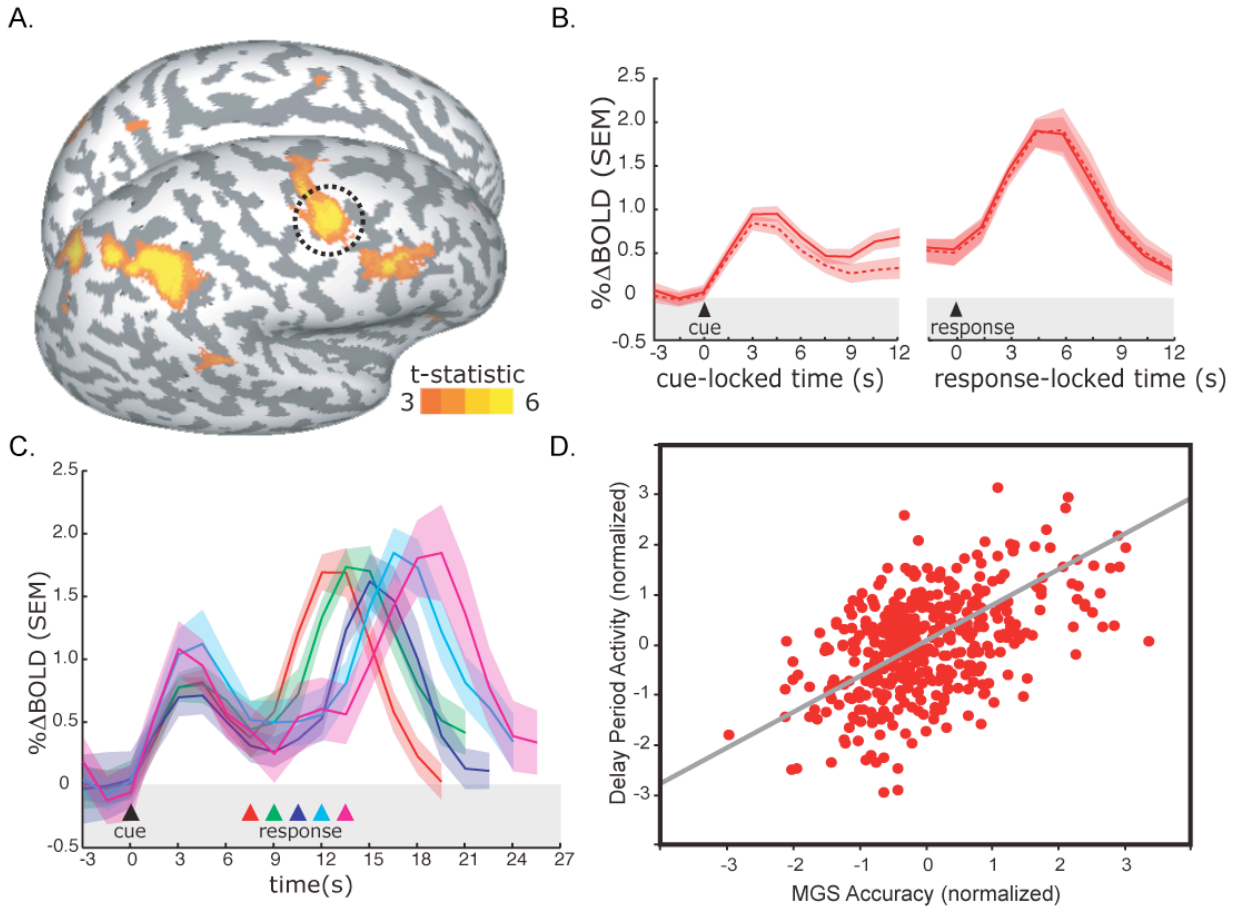

Figure 2. The functional homologies between monkey area FEF and putative human area FEF during a spatial memory-guided saccade task (MGS). A. BOLD activity during a memory delay period localizes to the precentral sulcus, the putative human FEF (circled). B. The time course of FEF BOLD activity persists above pretrial baseline during the delay period and is greater in the hemisphere contralateral (solid line) compared to ipsilateral (dashed line) to the location of the memoranda. C. FEF BOLD activity persists above baseline for the duration of the memory delay. Each colored line is a different delay length, ranging from 7-13.5 seconds. D. The magnitude of the delay period activity predicts the later accuracy of the memory guided saccade; greater BOLD predicts greater accuracy. A-C from Srimal & Curtis, 2008; D. from Curtis et al., 2005.

may be the source of the inhibitory post-synaptic potentials (Schlag, Dassonville, & Schlag-Rey, 1998). In any event, researchers should not assume, but instead measure the ways in which their BOLD data is similar to and different from existing monkey electrophysiology data. Testing this assumption is the first step in translational research.

Translation in action - In the exercise above, one can appreciate the successes made in translating and testing animal models of spatial working memory based upon electrophysiology studies in monkeys to the human using neuroimaging. Now let us turn to another example of successful translation, the inhibition of an unwanted saccade. A major goal of systems neuroscience is to understand the mechanisms by which we voluntarily control our actions. Control is necessary when the optimal response is uncertain or when prepotent responses must be inhibited. The well-characterized oculomotor system has been used to test several hypotheses about

motor control. Two laboratory analogs of behavioral inhibition have been most successful at uncovering the neural mechanisms of saccade control, the antisaccade task and the stop-signal task.

Antisaccade and Stop-Signal Tasks - In an antisaccade task (Hallett, 1978), subjects make a saccade (i.e., shift their gaze with a rapid ballistic eye movement) to the opposite hemifield, away from a visually-cued location. Correct performance requires that the subject first, inhibit the "reflex-like" prepotent tendency to shift their gaze to the visual cue and second, generate a saccade to the mirror imaged location of the cue. Prosaccade trials, where gaze is simply shifted to the visual cue, are commonly performed in separate blocks or randomly intermixed with antisaccade trials. Compared to prosaccades, antisaccades are slower due to the extra time required to inhibit the automatic saccade plus the time to program the antisaccade. Errors on antisaccade trials are characterized by hypometric saccades generated towards the visual cue. These errors are thought to reflect inhibitory failures because a corrective antisaccade is almost always generated, indicating an awareness of the task demands.

Stop-signal or countermanding tasks (Logan, 1994), as they are called, require the voluntary control over the production of movements because an imperative stop signal is infrequently presented instructing the subject that the planned movements should be withheld. In a stop-signal task, subjects make a speeded response, for example, an eye movement, upon the presentation of a visual go cue. On rare trials, just after the presentation of the go cue, an imperative stop signal is presented instructing the subject to withhold the planned movement. Intuitively, as the stop signal is delayed, the motor plan has more time to evolve toward execution, and the probability that the subject will be able to inhibit the response decreases.

Both tasks require withholding a prepotent response, but they differ in terms of when in the perception-action cycle inhibition is thought to begin. During a stop-signal task, inhibition begins late, after the go cue has been presented and therefore during the planning of the motor response. During an antisaccade task, before a block or before a trial the subject must be instructed whether the trial is an antisaccade or prosaccade trial. Therefore, inhibition can begin early, as soon as the subject is cued that the trial is an antisaccade trial.

Background: Electrophysiology of Monkey FEF - To understand what we might expect from neuroimaging studies of antisaccade and stop-signal task performance, we will first briefly review what we know from monkey electrophysiological studies. Then, we will discuss how well these findings have translated to humans using functional imaging.

Electrophysiological studies of the monkey frontal eye field (FEF) have yielded promising clues to the neural mechanisms of saccade control (see also Chapter by Johnston and Everling in the current volume). As reviewed in the chapter by Johnston and Everling, FEF neurons are traditionally thought to play a critical role in transforming visual information into saccade commands (Bruce, et al., 2004). FEF *saccade-type* neurons respond just prior to the execution of a saccade into the neuron's response

field. Electrical microstimulation of FEF saccade neurons evoke saccades with specific movement vectors. Moreover, the stochastic variability in saccade initiation is proportional to the time it takes the firing rate of these FEF neurons to reach a fixed threshold (Thompson, Bichot, & Schall, 1997). Therefore, FEF saccade neurons control the production of saccades (Schall, 2002). Another class of FEF neurons, *fixation-type*, are active when a monkey is actively fixating gaze on a stationary position. Microstimulation of FEF fixation neurons during the course of smooth pursuit or saccadic eye movements immediately halts oculomotion (Burman & Bruce, 1997). In summary, saccades are produced when activity in FEF saccade neurons increases and activity in FEF fixation neurons decreases (Everling & Munoz, 2000; Hanes & Schall, 1996; Munoz & Fecteau, 2002).

Antisaccade Task - With these two different types of FEF neurons in mind, now let us consider the behavior of FEF saccade and fixation neurons during prosaccade compared to antisaccade trials. Saccade neurons in the monkey FEF exhibit a greater firing rates prior to prosaccades compared to antisaccades (Everling & Munoz, 2000). Moreover, the difference in firing rate can be seen as early on well before the peripheral target even appears. Fixation neurons in the FEF exhibit a greater firing rate just prior to antisaccades compared to prosaccades, again hundreds of milliseconds before the appearance of the target. Therefore, on antisaccade trials when the animal anticipates that he will need to inhibit the prepotent reflex-like saccade, the firing rate of FEF saccade neurons decreases while the firing rate of fixation neurons increases. These changes are thought to bias the oculomotor system towards a less motile state where the onset of the target and its associated capture of attention is less likely to result in an unwanted saccade (Munoz & Everling, 2004). If activity in saccade neurons can be kept below a critical threshold just long enough for the voluntary antisaccade to be programmed and initiated, then the decision to make a correct antisaccade is likely to be achieved. Indeed, activity in FEF saccade neurons is greater on trials in which the animal failed to inhibit the saccade towards the target (Everling & Munoz, 2000).

Therefore, with these observations we can posit a simple neuronal mechanism that determines the ability to inhibit an unwanted saccade. At the time when the peripheral visual target stimulus appears, competition between FEF gaze-holding and gaze-shifting mechanisms determines whether a reflexive saccade is triggered or not. Moreover, the difference in firing rate between prosaccade and antisaccade trials, and the difference in firing rate between successful and failed antisaccades trials, can be seen several hundred milliseconds before the visually guided saccade must be inhibited. These competitive interactions may give rise to a psychological preparatory set that primes the oculomotor system towards a gaze holding or shifting state. Stochastic fluctuations in the firing rates of FEF neurons may destabilize the preparatory state leading to failures in the ability to inhibit the unwanted prosaccade.

Functional MRI studies have provided critical support in humans for the findings from monkey electrophysiology. First let us consider fMRI studies of antisaccades. Replicated many times now, the production of antisaccades compared to prosaccades causes *greater* BOLD activation in the human FEF (Brown, Goltz, Vilis, Ford, &

Everling, 2006; Brown, Vilis, & Everling, 2007; Cornelissen, et al., 2002; Curtis & Connolly, 2008; Curtis & D'Esposito, 2003; Ettinger, et al., 2005; Ford, Goltz, Brown, & Everling, 2005; Matsuda, et al., 2004; McDowell & Clementz, 2001; O'Driscoll, et al., 1995; Sweeney, et al., 1996). This may seem counter to what one might predict since the monkey electrophysiology has shown that firing rates are *lower* in FEF prior to antisaccades compared to prosaccades (Everling & Munoz, 2000). However, fMRI does not have the spatial resolution to measure activity from saccade and fixation neurons independently. Therefore, the increase is presumably due to the co-activation of saccade and fixation neurons in the FEF just prior to and during saccade production. BOLD signal in FEF is thought to be higher during antisaccade trials compared to prosaccade trials because of the increased activity of fixation neurons. Additionally, the processes related to inverting the saccade vector to the visual cued location may also contribute to increased BOLD activity during antisaccade trials. Finally and in general, saccades that are endogenously guided (i.e., antisaccades and memory-guided saccades) evoke greater BOLD activation than exogenous or visually-guided saccades. For all of these reasons, it has been challenging for researchers to unambiguously identify the neural mechanisms underlying the BOLD signal changes during antisaccade tasks.

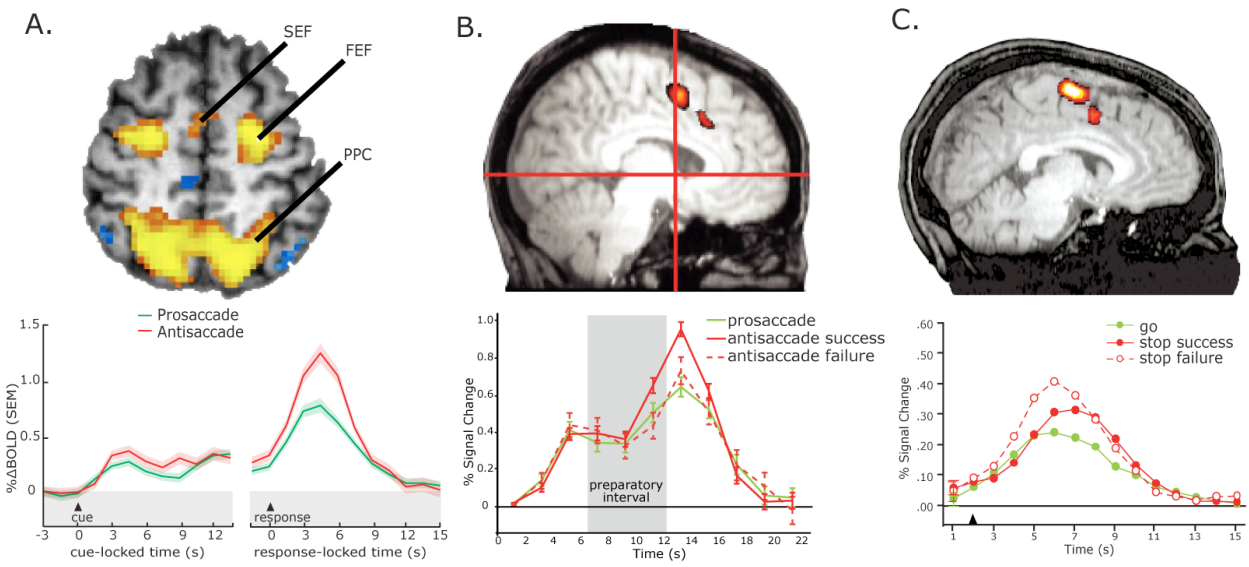

Figure 3. Functional imaging of saccade inhibition. A. Performance of antisaccade trials evokes greater BOLD activation than prosaccades in the FEF, SEF, and posterior parietal cortex (PPC). Top: Significant antisaccade greater than prosaccade activation is overlaid on an axial slice through dorsal cortex (Brown et al., 2007). Bottom: BOLD time course from FEF during antisaccade and prosaccade trials. The task instruction (trial type) was given at the "cue" period prompting the subject to prepare to make a prosaccade or antisaccade from a visual target presented at the "response" period. Notice that BOLD signal increased to a greater extent for antisaccades compared to prosaccades shortly after the cue was given (Curtis & Connolly, 2008). B. Saccade production activates the SEF (and anterior cingulate) as shown in the sagittal image (top). The time course of SEF BOLD activity ramps up during the preparatory period and is greater prior to correct than incorrect antisaccades, which are similar to prosaccades (bottom) (Curtis & D'Esposito, 2003). C. The SEF, depicted in the top sagittal image, show BOLD activation during the performance of an oculomotor stop-signal task. Time courses from the SEF show that activity is enhanced during stop trials when inhibition is successful and unsuccessful compared to go trials (Curtis et al., 2005).

To address these ambiguities, researchers have turned to event-related fMRI designs that can estimate BOLD signal arising from preparation epochs separate from saccade generation epochs. Recall that inhibition related processes can be marshaled as soon as the antisaccade instruction is given. These processes are thought to prepare the oculomotor system for the forthcoming conflict between the automatic programming of a saccade towards the impending visual stimulus and the controlled programming of an antisaccade. The human FEF and supplementary eye field (SEF; located in the anterior bank of the paracentral sulcus) have both been shown to increase in activity more during a preparation interval following an antisaccade instruction compared to a prosaccade instruction (Brown, et al., 2006; Brown, et al., 2007; Cornelissen, et al., 2002; Curtis & Connolly, 2008; Curtis & D'Esposito, 2003; Ford, et al., 2005) (Figure 3A). Importantly, the amount of SEF activity in the preparation interval prior to antisaccades predicts if the subject will later be successful at inhibiting the unwanted saccade to the prepotent visual target (Curtis & Connolly, 2008; Ford, et al., 2005) (Figure 3B). An identical pattern of results has been found using electrophysiological recordings from neurons in the monkey SEF (Schlag-Rey, Amador, Sanchez, & Schlag, 1997). Moreover, BOLD signal in the human SEF is greater in advance of antisaccades compared to prosaccades whether or not the location of the visual cue is known to the subject during the preparatory interval (Curtis & Connolly, 2008). Therefore, advance knowledge of the precise metrics of the forthcoming saccade does not abolish the need for inhibitory control. The putative roles of the FEF and SEF in the antisaccade task are different as evidenced by different patterns of BOLD activity. Activity in the FEF is consistent with neural changes tied to the competition between saccade and fixation neurons, the determinants of eventual behavior. Activity in the SEF is consistent with a higher level role in oculomotor control. For instance, SEF neurons may reduce the excitability of the oculomotor system through its connections with saccade and fixation neurons in the FEF (M. T. Lu, Preston, & Strick, 1994; Luppino, Matelli, Camarda, & Rizzolatti, 1993; Parthasarathy, Schall, & Graybiel, 1992; Schall, Morel, & Kaas, 1993; Shindo, Shima, & Tanji, 1995); more on this below).

Stop-Signal Task - The voluntary control of behavior, of which withholding an action is a critical demonstration, can be exerted at any point along the series of processes that evolve over time from sensation to action. In the context of a stop-signal task, inhibition takes place far downstream in this evolution, after the movement has been planned. Inhibiting or canceling a planned movement following an imperative stop signal can be modeled as a race between independent GO and STOP mechanisms (Hanes & Carpenter, 1999; Logan & Cowan, 1984). Which process first reaches a critical threshold, or finish line, determines whether the planned response is generated or not. By adjusting the time between the presentation of the stimulus that initiates the GO response processes and the presentation of the stop stimulus, an interval known as the stop signal delay, the probability that either one of the two possible responses will win the race can be adjusted (Logan, 1994). Canceling is easier when the stop signal delay is short because one has more time to cancel the movement. Importantly, using the saccadic response time distribution for GO trials and the probability of successful saccade cancellation at different stop signal delays, one can estimate the time needed

to cancel a planned saccade once the stop signal had been given; this time is referred to as the *stop signal reaction time* (SSRT).

The presaccadic growth of activity in FEF saccade neurons is correlated with saccade production while the growth of activity in FEF fixation neurons is correlated with saccade withholding during the performance of stop-signal tasks (Schall, 2001). FEF saccade neurons show a phasic burst of activity within 100 ms following the appearance of the visual target, while FEF fixation neurons activity declines rapidly (Schall & Hanes, 1998). These early changes in neuronal firing reflect the planning and preparation of the visually guided saccade. When no stop-signal is emitted (i.e., GO trials) the firing rate of saccade neurons continues to build until the critical threshold is reached and a saccade is finally generated. When a stop-signal is emitted (i.e., STOP trials) and the animal is successful at inhibiting the planned saccade, fixation neurons exhibit a burst of firing that coincides with a sharp decrease in the firing rate of saccade neurons. However, if these changes in firing invoked by the stop signal do not occur quickly enough, or to be more precise, do not occur within the SSRT, then the animal is not able to withhold the movement and a failure of inhibition occurs. Overall, the activity pattern of FEF saccade and fixation neurons corresponds very well with the hypothetical GO and STOP processes of the race model where the outcome of a race between saccade and fixation neurons determines whether or not a saccade is generated.

Functional imaging studies of oculomotor stop-signal task performance have been supportive of these animal models (Curtis, Cole, Rao, & D'Esposito, 2004; Leung & Cai, 2007). The successful cancellation of a planned saccade (i.e., STOP trial) causes greater human FEF activation than the generation of a saccade on no-stop signal, or GO, trials (Curtis, Cole, et al., 2004; Leung & Cai, 2007) (Figure 3B). Similar to the reasoning used to understand the increased activation during antisaccade compared to prosaccade trials, the increased activation likely reflects the co-activation of saccade and fixation neurons on STOP trials, which would evoke great BOLD signal than trials in which there were no stop signal. Above, it was suggested that the SEF plays a critical role in preparing the oculomotor system for conflict prior to antisaccades. Additionally, there must be a mechanism that allows animals to monitor their performance such that strategic changes can be implemented. Detecting the production of errors is necessary for one to make adaptive changes in future behavior. Neurons in the monkey SEF show a pattern of activity during stop-signal tasks that suggest that they may play an important role in monitoring performance. Some SEF neurons show a burst of activity following errors on STOP trials and some show a burst of activity following successfully cancelled STOP trials (Stuphorn & Schall, 2002; Stuphorn, Taylor, & Schall, 2000a). Note that the onset of the activity is after the SSRT so these signals are too late to be critically involved in the act of inhibition. Instead, they signal how successful or not the animal is performing the required task. From fMRI studies of humans, we know that BOLD activity in the human SEF is greater for both successful and unsuccessful STOP trials compared to GO trials (Curtis, Cole, et al., 2004). This suggests that the human SEF contains the requisite signals for monitoring performance that could be used in feedback learning. Presumably, these signals cause changes in the oculomotor system

by biasing the activity of saccade and fixation neurons on the next trial similar to the way in which it might bias activity when preparing to make an antisaccade.

As we can see from these studies, during oculomotor tasks that require inhibiting unwanted saccades, neurons in the FEF that code for mutually exclusive gaze shifts may compete for expression. Moreover, the SEF may provide control signals that can be used to optimize performance. These include increased activity when one anticipates and prepares for conflicting oculomotor responses and activity that signals both successes and failures inhibiting the unwanted responses.

Conclusions - In this review, I described both the challenges to and the successes in using fMRI to test models of oculomotor control. Imaging studies have provided key evidence in support of several models of saccade control that were developed with electrophysiological data recorded in monkey oculomotor areas. Testing these animal models of human cognition in humans is a necessary translational step whose importance cannot be underestimated.

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