What can fMRI tell us about functional variability in the oculomotor system and saccade performance?

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The oculomotor system is well characterized in terms of both motor behavior and neural circuitry. Consequently, it provides a useful framework for understanding neural similarities and differences in humans. Although variability in the performance of saccade-related tasks is readily observed within and across individuals, little is known about the neural properties that determine these differences.

Numerous areas throughout the forebrain, midbrain, and brainstem are involved with visual fixation and saccadic eye movements (reviewed by McDowell et al. 2008). The functional properties of these areas can be examined using paradigms such as the gap task and overlap task. In the gap task, the subject is instructed to focus on a fixation point and look toward a peripheral target when it appears. There is a short delay (gap) between the fixation point disappearing and the target appearing. In the overlap task, the subject is instructed to focus on a fixation point and look toward a peripheral target when it appears, despite the continued presence of the fixation point. An experimental advantage of the gap task is that it may produce short latency saccades (express saccades).

Cortical areas, such as the frontal eye field (FEF), prefrontal cortex, and superior parietal lobe (SPL), and the basal ganglia are believed to have a role in modulating saccade behavior in a goal-oriented manner (reviewed by McDowell et al. 2008). These areas are also involved in cognitive processes such as attention and task selection (reviewed by Corbetta and Shulman 2002), suggesting that they may be particularly important in determining inter- and intraindividual variability in behavior.

In a recent study published in the Journal of Neurophysiology, Ozyurt and Greenlee (2011) used fMRI to examine cortical and striatal activation related to inter- and intraindividual variability in the performance of saccade tasks. The authors hypothesized that increased activation in fronto-parietal regions would be linked to faster gap task performance and that increased activation in the FEF and caudate nucleus would be linked to faster overlap task performance. Eighteen healthy human subjects were presented with the gap and the overlap tasks in pseudo-randomized order during event-related BOLD fMRI acquisition. The events of interest for the gap and overlap paradigm, respectively, were the gap onset time and the target onset time.

Results indicated considerable interindividual variability in mean saccadic reaction time (SRT) for both the gap and overlap tasks (Fig. 2 in Ozyurt and Greenlee 2011). In the gap task, longer SRT was associated with greater preparatory activation in the right FEF and bilateral SPL in the interindividual analysis, and with greater activation in the left SPL/precuneus in the intraindividual analysis. Alternatively, in the overlap task, shorter SRT was associated with more preparatory activation in the bilateral inferior frontal junction (IFJ) and a cluster in the head of the right caudate nucleus in the interindividual analysis, and longer SRT was associated with greater activation of right inferior frontal gyrus (IFG) in the intraindividual analysis.

Accordingly, Ozyurt and Greenlee (2011) suggested longer SRTs in the gap task were a result of inhibitory signals that were reflected by increased FEF activation. For the overlap task, the authors suggested shorter SRTs were a result of the involvement of the IFJ in facilitating task switching and cognitive control. Furthermore, they suggested that increased right IFG activation was associated with slower performance because activation in this region reflects the inhibition of motor processes.

In this paper, we comment on the differences between the studies of inter- and intraindividual variability conducted by Ozyurt and Greenlee (2011), and, using their FEF results, we discuss the use of fMRI and the meaning of the BOLD signal. Our goals are to highlight the contributions of Ozyurt and Greenlee with a critical consideration of the methodology in the context of other studies and to suggest ways to further study the neural correlates of variability in oculomotor performance.
Inter- vs. intraindividual variability. Ozyurt and Greenlee (2011) used two different approaches to study variability in oculomotor function. In the interindividual analysis (simple regression), SRT and BOLD activation strength were averaged across all trials for each individual and were then correlated with one another. In contrast, in the intraindividual analysis (parametric modulation) the BOLD response was modelled separately for each trial based on SRT, thus taking trial-to-trial variability into account. Since these two analyses address questions about two different types of variability, it is important to consider distinct implications for each analysis.

Intraindividual and interindividual variability in oculomotor performance are likely due to different factors. For example, neuroanatomical differences in oculomotor regions between subjects may underlie inter- but not intraindividual functional variability. Increasing evidence suggests that interindividual variability in gray matter volume and white matter connection strength is predictive of motor and cognitive function, including motor response reaction times and speed-accuracy decision making (reviewed by Kanai and Rees 2011). Thus, a consideration of differences in neuroanatomy could be useful for interpreting the functional findings.

However, at the intraindividual level, neuroanatomy presumably remains unchanged over the course of a short experiment. Trial-to-trial differences in performance are likely due to fluctuations in attention and the corresponding changes in brain activity during a task (Cohen and Maunsell 2011). Furthermore, the intraindividual variability that was observed by Ozyurt and Greenlee (2011) may have been influenced by the study’s pseudo-randomized design. A previous trial could affect the allocation of attentional resources during the current trial and thus affect performance. It is well established that the task category of a trial can affect reaction time on the next trial for tasks such as gap and memory saccades (reviewed by Fecteau and Munoz 2003). Disentangling the source of intraindividual variability in performance would provide a framework for understanding the neural activation associated with this variability. Since the interindividual analysis may address questions more closely related to neuroanatomy than the intraindividual analysis, it is unsurprising that Ozyurt and Greenlee (2011) obtained largely dissimilar results for the two analyses conducted on the same data.

The BOLD signal and the FEF. Ozyurt and Greenlee (2011) expected FEF activation to be negatively correlated with SRT in both the gap and overlap tasks, but FEF activation was only found to be positively correlated with SRT in the gap task. The authors suggested two explanations for the lack of significant FEF results. First, activation in the time required to initiate a saccade may not have been detected because of the limited temporal resolution of fMRI. Second, the effect of preparatory processes on saccades across the range of SRTs may be similar, and thus no difference in activation was observed.

The FEF contains both saccade-related neurons and fixation-related neurons (reviewed by Hanes et al. 1998), and this offers a third explanation. The activity of saccade-related neurons would be higher relative to the activity of fixation-related neurons in low SRT trials while the opposite would occur for high SRT trials. While the degree of activity in these neuron populations may differ over a range of SRTs, the overall activity (the sum of saccade-related and fixation-related activity) at any given SRT may be similar. Since BOLD signals are derived from the pooled activity of multiple neurons, fMRI lacks the spatial resolution to dissociate distinct neuron populations in the same brain area (Heeger and Ress 2002). Consequently, correlations to specific neuronal activity may be difficult to observe.

In the gap task, Ozyurt and Greenlee (2011) suggested inhibitory signals, and thus increased activity from fixation-related neurons, may have produced the increased FEF activation associated with longer SRTs. However, this interpretation may overlook noninhibitory preparatory processes. Saccade-related activity and other processes may be masked by inhibitory activity. More importantly, fMRI may be biased toward certain types of neuronal activity. In contrast to single neuron recordings, which favor recording pyramidal cells, the BOLD signal may be influenced more strongly by fast-spiking, synchronized, task-modulated inhibitory interneurons (Ford et al. 2009; Mitchell et al. 2007). There is also evidence that BOLD signals may better reflect input and synaptic processing than action potential output (Heeger and Ress 2002; Logothetis et al. 2001).

Ultimately, the findings of Ozyurt and Greenlee (2011) highlight the caution that is required when interpreting BOLD signals or creating functional imaging hypotheses that are based on single neuron electrophysiology. fMRI and electrophysiology experiments have been shown to produce both congruent and incongruent results, and it is important to understand the similarities and differences between fMRI measurements and neuronal signals (Heeger and Ress 2002).

Future directions. Regardless of the limitations of fMRI and the caution needed to interpret its results in the context of electrophysiology, the findings of Ozyurt and Greenlee (2011) pose important questions regarding inter- and intraindividual variability in oculomotor performance. Future studies should carefully consider the separate questions that interindividual and intraindividual analyses address. To study interindividual variability, future studies could examine the link between anatomical and functional variability with respect to oculomotor performance. An approach to understanding intraindividual variability could involve the study of fluctuations in brain activity in oculomotor-related regions before the task is initiated. Trial-by-trial fluctuations in pre-stimulus activity have been shown to predict many domains of behavior and perception (reviewed by Northoff et al. 2010), and it is possible that this type of predictability extends to oculomotor behavior.

Conclusion. While the neurophysiology of the oculomotor system has been characterized extensively, much remains to be learned about the variability in saccade performance that is observed within and across individuals. Since most fMRI studies seek to characterize overall effects within populations and treat variability as noise, the study by Ozyurt and Greenlee (2011) represents an important step forward in understanding how oculomotor circuitry functions differently in different brains and in different contexts. Ultimately, this study provides a foundation for future studies and highlights the importance of investigating both function and anatomy to elucidate the mechanisms of inter- and intraindividual variability.

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