Published in final edited form as:
Neuroimage. 2007 ; 36(Suppl 2): T54–T60. doi:10.1016/j.neuroimage.2007.03.018.

fMRI Studies of Eye Movement Control: Investigating the Interaction of Cognitive and Sensorimotor Brain Systems

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Abstract

Functional neuroimaging studies of eye movement control have been a useful approach for investigating the interaction of cognitive and sensorimotor brain systems. Building on unit recording studies of behaving nonhuman primates and clinical studies of patients with a focal brain lesion, functional neuroimaging studies have elucidated a pattern of hierarchical organization through which prefrontal and premotor systems interact with sensorimotor systems to support context-dependent adaptive behavior. Studies of antisaccades, memory guided saccades, and predictive saccades have helped clarify how cognitive brain systems support contextually guided and internally-generated action. The use of cognitive and sensorimotor eye movement paradigms is being used to develop a better understanding of lifespan changes in neurocognitive systems from childhood to late life, and about behavioral and systems-level brain abnormalities in neuropsychiatric disorders.

Introduction

Behavioral studies of eye movement control in the laboratory environment have provided many important insights into how the brain integrates perception and action planning. This line of work was initiated and continues to be actively pursued in studies of behaving nonhuman primates. Studies with monkeys, together with findings from clinical studies of patients with focal brain lesions, created a rich framework for using functional neuroimaging for further developing understanding of visuomotor systems in the primate brain.

Early work in this area sought to map regions in the human brain that are functionally homologous to those that had been well characterized in the monkey based on neuronal stimulation and unit recording studies. One initial unexpected finding from this work was the repeated demonstration that the human frontal eye field (FEF) appeared to be located in the precentral sulcus, more posterior than where earlier electrical stimulation studies during neurosurgery had placed the region. The consistency of the observation of FEF localization eventually led to consensus about the issue, though controversy remains about potential functional differences between the dorsomedial and ventrolateral aspects of the precentral

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sulcus. Cytoarchitectural studies eventually determined cellular-level commonalities between this area of the precentral sulcus and prior reports from monkey FEF. Importantly, the Rosano et al. (2003) studies with neurofilament protein stains showed that layer IV of prefrontal cortex was evident back to the rostral rim of the dorsal precentral sulcus, which is consistent with monkey studies localizing the FEF at the junction of premotor and prefrontal cortex.

Another line of work showed further consistency in organization of monkey and human FEF, and illustrated the potential contribution of very high-resolution functional magnetic resonance imaging (fMRI) studies for finely mapping functionally distinct brain regions. Primates use two kinds of eye movements for foveating objects of interest, each supported by different neural systems. Saccadic eye movements are used to rapidly shift gaze between static objects of interest, while smooth pursuit eye movements allow the eyes to sustain focus on slowly moving objects. In the monkey brain, the smooth pursuit and saccade regions of FEF are spatially segregated, with the pursuit area located at the fundus of the arcuate sulcus and the saccade region along the rostral wall. Early human fMRI studies, conducted at lower spatial resolution, failed to separate these regions which appeared to have extensive overlap. Rosano et al. (2002) used high resolution fMRI (0.8mm by 1.6mm in plane resolution) to demonstrate a specific pattern of activity in the precentral sulcus with a saccade region along the rostral wall and a pursuit area near the fundus. This pattern parallels the organization of FEF in the monkey arcuate sulcus.

Other studies have contributed to the localization of other oculomotor areas in the human brain including lobules VI and VII in the cerebellar hemispheres, the oculomotor cerebellar vermis, the supplementary eye fields (SEF), along the medial wall in the interhemispheric fissure rostral to the supplementary motor area (SMA) and caudal to the presupplementary motor area, and the parietal eye fields in the posterior aspect of the intraparietal sulcus. The parietal areas are important for spatial attention and spatial coordinate transformations (Merriam et al., 2003), and areas in the cerebellum are important for motor learning (Desmurget et al., 2000).

Cortical Control of Higher Motor Cognition

When shifts of gaze need to be initiated based on contextual cues, additional neural regions are recruited to support saccade initiation. Heteromodal neocortical regions support such higher level cognitive abilities, although the striatum and more prototypically sensorimotor regions are also critically important for supporting the cognitive control of gaze.

Antisaccades—One widely used task for evaluating the voluntary control of saccades is the antisaccade paradigm. During antisaccade trials, subjects are instructed to generate a saccade to the mirror location of a peripheral target. This requires subjects to suppress the “visual grasp reflex” to look to a suddenly appearing target, and instead shift gaze away in the opposite direction. Different neural circuitries are now believed to support these two different task requirements.

Neurophysiology and human lesion data indicate that activity in dorsolateral prefrontal cortex (DLPFC) is involved in the inhibitory component of antisaccade tasks. Some DLPFC neurons fire specifically to anti-cues. Hasegawa et al. (2004) identified a class of “don’t look” cells in prefrontal cortex which were associated specifically with anti-targets. Also, high rates of failure to suppress saccades to targets are found in patients with DLPFC lesions, but not those with lesions of the frontal and parietal cortical eye fields.

Functional brain imaging studies also indicate a DLPFC involvement in response inhibition on anti-tasks, including those using positron emission tomography (PET), fMRI, and electro- and magneto-encephalography (EEG/MEG). Of importance, this inhibition-related DLPFC

activity appears to precede response generation and is specific to trials where subjects correctly perform the anti-saccade task.

The exact computations supported by DLPFC relevant for correct antisaccade task performance remain to be specified. DLPFC is known to be involved in integrating perception and action planning by, for instance, using learned rules to guide behavior. Thus, antisaccade-related DLPFC activity may be contributing to the response selection process. DLPFC activity during such tasks may support a preparatory set to suppress saccades to new targets. There is also evidence for increased activity associated with correct antisaccade trials in the vicinity of FEF (specifically the dorsomedial FEF), SEF, presupplementary eye fields (pre-SEF), and anterior cingulate cortex. The anterior cingulate is most likely involved with conflict detection and error monitoring during such tasks.

The internal coordinate system transformation and then use of that transformation to generate a saccade away from the target may depend on posterior parietal cortex, while the volitional saccade generation process during anti-saccade tasks appears to depend primarily on dorsomedial FEF and SEF. Efforts to clarify what brain regions are involved in the coordinate transformation process for antisaccades will benefit greatly from multimodal neuroimaging studies (fMRI and MEG/EEG), and translational research involving single unit data from behaving nonhuman primates. Ultimately, this line of work will help explain how prefrontal systems interact with sensorimotor systems in a hierarchical manner to support behavioral flexibility and context-appropriate adaptive behavior.

Oculomotor Delayed Response (ODR) Tasks—ODR paradigms (also referred to as memory guided saccade tasks) are used to assess maintenance processes in spatial working memory. During ODR tasks, subjects are instructed to remember the location of a briefly presented visual target through a delay period during which the visual cue is no longer present, and then later initiate a saccade to the remembered location. Neurophysiological evidence from monkey studies indicates that DLPFC supports ODR performance. In humans, lesions of DLPFC disrupt the ability to perform this task. Imaging studies demonstrate increased activity in DLPFC associated with performance on delayed response tasks.

Similar to the antisaccade task, DLPFC circuitry supports the ability to properly perform ODR tasks, working in an integrated way with sensorimotor areas in the cortical eye fields to support correct ODR performance. The supplementary eye field appears to play an especially significant role in the initiation of memorized sequences of saccades (Heide et al., 2001). On the one hand, the overlap in the distributed basal ganglia-thalamocortical circuitry supporting both antisaccade and ODR performances may be a manifestation of common visuospatial attention demands of both tasks. On the other hand, there are indications that areas in DLPFC, FEF, parietal eye fields and extrastriate areas are supporting specific cognitive operations in these two tasks. How DLPFC and sensorimotor control regions work in unison to support component cognitive operations of working memory tasks is an active area of research.

Procedural Learning Tasks—Visually tracking a stimulus that repeatedly alternates between two or three fixed positions at a fixed time interval has been used as a paradigm for evaluating motor or procedural learning. Subjects quickly learn the predictability of the target motion and generate anticipatory saccades that are initiated before illumination of the next target. Rapid changes in the brain circuitry supporting the shift from visually-guided to anticipatory/predictive saccades over a period of seconds is a form of learning that is amenable to investigation in a single fMRI study.

Single unit studies show that greater FEF activity before a predictive/anticipatory saccade is associated with shorter saccadic reaction times, and patients with FEF lesions have difficulty

generating anticipatory saccades. PET studies showed changes in FEF, SEF, and extrastriate areas during predictive tasks. In an fMRI study of saccades to predictable targets, Gagnon et al. (2002) reported that FEF activity was greater during predictive tracking when compared with fixation or visually guided saccades, and that FEF activity increased over time as the predictability became apparent. In a study describing the functional dissociation between lateral and medial FEF, Simo et al. (2005) contrasted a predictive saccade task with known timing and direction with an unpredictable visually-guided saccade task. During predictive tracking there was more activity in pre-SMA, pre-frontal, inferior parietal and anterior cingulate cortices, and in dorsomedial thalamus and hippocampus, and less activity in occipital cortex, superior parietal lobule and medial FEF. These data are consistent with a lateral-medial FEF distinction made in a recent fMRI study contrasting activity between new and familiar saccade sequences. Thus, saccades to predictable target appearance, generated by learned cognitive plans rather than sensorimotor systems responding to the appearance of a visual stimulus, show a fundamentally different pattern of brain activation.

The learning of saccade sequences invokes procedural learning and a change from sensory- to memory-driven neural circuitry. Research has focused on the role of SEF in these tasks because supplementary motor regions are important for motor sequence learning. In monkeys, presaccadic firing of SEF cells changes with the rank order of a saccade within a sequence. Lesions of SEF result in difficulty generating saccade sequences. Petit et al. (1996, 1997) showed that learned saccade sequences were associated with increased sequence-related activity in SEF, intraparietal cortex, superior frontal sulcus, and precuneus. A more recent fMRI study, which was designed to emphasize the transition from sensory to memory-driven circuitry, juxtaposed well-practiced with newly acquired saccade sequences. The data showed greater activity associated with newly learned sequences in precuneus and pre-SEF, an area that may be of greatest importance in facilitating sequence acquisition.

Oculomotor Studies of Neurocognitive Development

Cognitive control underlying problem solving and reasoning abilities continues to develop during adolescence supported by improvements in voluntary response suppression and working memory. These improvements occur concurrently with brain maturational changes, including synaptic pruning and myelination, which support efficient neuronal processing and functional integration. These changes in brain maturation occur throughout association areas of neocortex.

The development of noninvasive fMRI provided an approach for advancing understanding of the neural basis of cognitive development. Cognitive studies have focused on the late development of prefrontal cortex during adolescence because of its importance in supporting response suppression and working memory abilities, processes that can be assessed with the antisaccade and ODR tasks respectively. Recent fMRI studies indicate that enhancements in widely distributed integrated brain systems are crucial for the development of prefrontal functions. Behavioral and neuroimaging studies have begun to delineate the trajectories of these developmental improvements and provide evidence for changes in brain function with maturity.

Development of Voluntary Response Suppression—Voluntary response suppression, the ability to filter out distracters and retain a preferred response set, is crucial for choosing optimal responses based on a cognitive plan over task-irrelevant alternatives. Voluntary response suppression develops throughout childhood and adolescence. While neuropsychological studies typically have indicated improvements through childhood, oculomotor tasks have shown continued maturation of the capacity for voluntary response suppression well into adolescence.

Several studies with large samples have now characterized performance in the antisaccade task from childhood through early adulthood. The latency to initiate an antisaccade, i.e. to suppress a saccade to a target and plan/decide to initiate a saccade away from the target, decreases with age and matures through adolescence. Decreases in response latency continue until 25 years of age, and intersubject variability also decreases in response latency stabilizes at approximately 20 years of age.

The ability to suppress a saccade to a visual target also shows dramatic developmental improvement in adolescence. Studies have found improvements from childhood, when subjects fail to suppress saccades to visual targets on approximately 50–60% of trials, to early adulthood when subjects make errors on only 10–20% errors. Error performance decreases until approximately age 15 and then stabilizes.

fMRI studies have begun to provide a characterization of the maturation of neural systems supporting antisaccade performance through development. Only one fMRI study to date has investigated developmental changes (ages 8–30) in brain function underlying improvements in antisaccade performance. All age groups demonstrated recruitment of a widely distributed circuitry including the frontal, supplementary, and parietal eye fields, dorsolateral prefrontal cortex, thalamus, and striatum. Children showed selective increases of activity in posterior parietal regions including the supramarginal gyrus, suggesting a reliance on visuospatial and attention processing rather than frontal lobe systems for voluntary behavioral planning. Adolescents, who performed similarly to adults, demonstrated greater activation of DLPFC and striatum than did the adults, suggesting a greater effort or computational activity is necessary for them to perform this task at adult levels. These results suggest that, from childhood to adolescence, there is increased recruitment of prefrontal cortex to regulate sensorimotor systems in a hierarchical manner, similar to what has been found in other developmental fMRI studies of response suppression using neuropsychological tasks. Only adults recruited the lateral cerebellum, which supports cognitive processes related to timing and learning, and is known to interact with prefrontal systems to support enhanced performance on some higher cognitive tasks.

Studies of elderly adults have also been conducted and reveal age-related declines in behavioral performance. Sweeney et al. (2001) found that performance on visually-guided saccade and antisaccade tasks was poorer in elderly (age 65–80) than young adults. In an fMRI study, Raemaekers et al. (2006b) found that relationships between frontal and parietal eye fields were altered during visually-guided saccades in adults between the ages 55–72 relative to young individuals.

Development of Working Memory—The developmental emergence of working memory is believed to underlie age-related improvements in many complex mental abilities. Working memory capacity improves through childhood and adolescence as reflected by improvements in memory span, working memory for spatial locations, manipulating and retaining visual information, retaining information on orientation of a pattern of figures, and the ability to maintain and manipulate multiple spatial units. In cross-sectional laboratory studies in which participants performed an ODR task, the accuracy of responses continued to improve into adulthood, showing adult levels of performance at approximately 19 years of age.

A widely distributed brain circuitry is known to underlie spatial working memory. Several fMRI studies have begun to explore the changes in brain function underlying developmental improvements in working memory. These studies used tasks requiring that subjects retain a spatial location or a sequence of non-spatial stimuli in memory and use this information to guide a future response. Findings suggest a transition from reliance on striatal regions in childhood to a more widely distributed circuitry including prefrontal, premotor, and posterior

parietal regions in adolescence. In an fMRI study of subjects between the ages of 8–47 using the ODR task, a shift from dependence on caudate nucleus and anterior insula in childhood to increased reliance on DLPFC and premotor regions was found. In that study, in adulthood, findings indicated a decreased reliance on DLPFC and the recruitment of regions that are not primary to working memory, but that may enhance performance, including ventrolateral prefrontal cortex and the supramarginal gyrus.

Taken together, developmental fMRI studies using oculomotor tasks have been informative about important developmental changes in cognitive and brain function. Notably, as the brain matures, more widely distributed circuitry appears to be recruited that may reflect increased functional integration in brain systems with resulting computational efficiencies.

Clinical Studies

Laboratory studies document abnormalities of oculomotor control in several neurological and psychiatric disorders. The extensive knowledge about cognitive and sensorimotor control in the oculomotor system has provided a useful foundation for using functional brain imaging for learning about abnormalities in brain disorders that are related to these impairments. Examples include a reduced accuracy of memory guided saccades on the ODR task in autism, and speeded saccade latencies in acutely ill medication-naïve first-episode schizophrenia patients that normalize with atypical antipsychotic medication. A worsening of ODR impairments and an improvement in antisaccade performance have been reported in treatment naïve first episode schizophrenia patients after antipsychotic treatment.

The illness most studied in fMRI eye movement paradigms to date is schizophrenia. This is reflected in the literature with laboratory studies of eye movement abnormalities as well. Interest of psychiatric researchers in oculomotor measurements in part reflects the need for sensitive quantitative approaches for investigating the more subtle brain changes associated with serious mental illness than with many neurological disorders. In smooth pursuit paradigms, differences have been found between schizophrenia patients and healthy individuals in brain areas that generate extraretinal signals predicting target velocity, which are needed to accurately match eye to target velocity (Nagel et al., in press). In studies of medicated patients, Tregellas et al. (2004) and Hong et al. (2005) found a lower level of activation in schizophrenia patients in frontal eye fields and anterior cingulate. Hong et al. (2005) also reported reduced activation in supplemental eye fields and posterior superior temporal cortex. Both studies further reported greater pursuit-related activation in medial occipital-temporal areas, as Lencer et al. (2005) described in extrastriate area MT. Keedy et al. (2006) examined an unmedicated first-episode schizophrenia patient sample during a smooth pursuit task in an fMRI study, and found reduced neocortical activation in several areas including frontal eye fields, supplementary eye fields, parietal eye fields, cingulate cortex, and precuneus.

Results from fMRI studies of schizophrenia patients performing visually guided saccade tasks follow a similar pattern of possible treatment effects. In unmedicated first-episode patients, Keedy et al. (2006) reported widespread reductions of task-related activation in frontal, supplementary, and parietal eye fields, cingulate cortex and precuneus, whereas studies of medicated schizophrenia patients have been equivocal. Raemaekers et al. (2002) reported similar but less extensive relative reductions in schizophrenia patients, and McDowell et al. (2002) reported no differences. These data, paralleling data with pursuit tasks, suggest that medication or enhanced psychological adjustment associated with clinical recovery may tend to normalize brain function related to eye movement control.

Visually guided saccade paradigms have also been used to study other patient groups in fMRI studies. Alzheimer’s disease patients displayed reduced right hemisphere dominance in the

parietal activations seen in matched healthy older individuals. Autistic adults have also been studied with visually guided saccade paradigms. In a relatively small sample of individuals with autism, Luna et al. (2002) did not find abnormalities in activation during visually guided saccades. However, during the oculomotor delayed response task, where laboratory studies had previously reported behavioral deficits, dorsolateral prefrontal cortex activity was reduced in the individuals with autism. This is consistent with the view that that this region is dysfunctional in autism in ways that contribute to working memory deficits in the disorder.

fMRI studies have also shown abnormalities among subjects with schizophrenia during cognitively complex tasks. In an antisaccade task, schizophrenia patients demonstrated less activation in right DLPFC. Raemaekers et al. (2006a) reported atypical striatal but not prefrontal activation during an antisaccade task in schizophrenia subjects, but antisaccade-related prefrontal cortex activation was not observed in their healthy controls, suggesting their paradigm did not recruit prefrontal circuitry activation. Both unmedicated and medicated schizophrenia subjects have been studied with the ODR task. Results of these studies demonstrated broadly reduced activation in basal ganglia-thalamocortical regions supporting sensorimotor and attentional components of eye movement control in schizophrenia. Both studies also found evidence of reduced DLPFC activation. While most studies have been conducted with medicated patients, an important avenue of future exploration is the examination of how medications change functional brain systems to improve attentional and other cognitive processes in patients with neuropsychiatric disorders.

Abnormalities observed in schizophrenia patients have been reported in the first-degree family members of patients with schizophrenia who have no personal history of the illness. In studies of smooth pursuit, antisaccades, and the oculomotor delayed response task, reduced activations in oculomotor circuitry have been reported in unaffected first degree relatives of schizophrenia patients. However, abnormalities are generally attenuated relative to findings in the patients. Overall, this work suggests that eye movement paradigms may be elucidating pathophysiology in functional neural systems that is associated with familial liability, and that fMRI studies of oculomotor function in patient populations have promise to provide new insights into the pathology underlying complex brain disorders.

Conclusions

Studies of eye movement control provide a promising approach for learning about sensorimotor and cognitive aspects of reflexive and voluntary action planning. Translational laboratory studies have provided considerable information about behavioral aspects of these systems. fMRI studies provide a noninvasive approach for learning about the brain systems that support these sensorimotor and cognitive functions. Importantly, this body of work can contribute significantly to the understanding of how these systems develop in healthy individuals, of abnormalities of these systems in brain disorders, and of how treatments alter the functional organization of brain systems to support more adaptive cognitive and behavioral functions.

One interesting observation from functional neuroimaging studies in this area has been the apparent hierarchical organization of function suggested across studies in this area. First, when subjects passively track moving targets or shift gaze to unpredictable target displacements, activation is robust in FEF, SEF, posterior parietal cortex, and cerebellum. When cognitive control of the system is required for responses based on internal plans such as in ODR, antisaccade and predictive learning paradigms, changes of activation in a frontostriatal loop including DLPFC, caudate nucleus, and dorsomedial thalamus are typically seen, in addition to activation in sensorimotor systems. This pattern of findings is consistent with unit recording studies of behaving monkeys. An important direction for future work in this area will be to

clarify how this hierarchical integration of prefrontal and sensorimotor systems varies across different types of task demands.

Understanding the functioning of a distributed cortical system requires collecting data with both high spatial and temporal resolution. Multimodal imaging studies (fMRI and MEG/EEG data on subjects performing the same tasks) may add significantly to our understanding of how prefrontal and sensorimotor systems interact to support behavioral control. Once achieved, this knowledge will provide powerful new tools for clinical and lifespan research.

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