The Prefrontal Cortex

The prefrontal cortex (PFC) is thought to be the most important brain area for higher-order cognition and sits at the apex of the sensory and motor hierarchies. The functions of the PFC give rise to higher-level cognitive abilities that make us uniquely human. They are also responsible for dysfunctions of the PFC that result in severe psychopathology, such as schizophrenia, attention deficit hyperactivity disorder (ADHD), substance abuse disorders, Alzheimer’s and Parkinson’s disease, and AIDS-related dementia. But despite its importance, we know very little about the mechanisms by which the PFC supports adaptive and maladaptive behaviors.

The long-term goal of the lab’s research is to understand the mechanisms by which the PFC supports higher-level cognition. Most theories of PFC function posit that the PFC plays an important role in cognitive control. Cognitive control or “executive control” processes help guide thought and behavior based on internally generated goals. Cognitive control is necessary when one must use internal representations to guide behavior because the current external environment does not provide the necessary information to help one make a decision, a process known as working memory. Cognitive control is also needed when one must override responses that may otherwise be automatically elicited by stimuli in the external environment. Our lab studies both of these types of cognitive control.

Working Memory

Arguably, all forms of higher-level cognition depend on our ability to create and maintain for short periods of time internal representations of information, a process known as working memory. Working memory allows animals to use information that is not currently available in the environment but is crucial for adaptive behavior. Without the ability to temporarily store information on-line, one’s behavior is stereotyped and largely depends upon learned stimulus–response associations. If, however, an internal representation of critical information can be created and maintained for a short period of time, flexible behavior emerges because one’s decisions can now utilize representations of temporally discontinuous events. Persistent neural activity during the delay period between a sensory cue (e.g., the position of a briefly flashed spot of light) and a later motor response (e.g., a shift of gaze to the remembered location) is the most compelling evidence that this activity reflects some form of a memory representation (Curtis and D’Esposito 2003a). In fact, essentially all models of working memory require the persistence of a representation (e.g., Wang 2001). Using fMRI, we have successfully identified several frontal and parietal areas that show persistent neural activity during memory delays (Curtis 2006; Curtis and D’Esposito 2006; Curtis et al. 2004; Schluppeck et al. 2006; Srimal and Curtis 2008) (Figure 1).
Nature of persistent neural activity

These studies have isolated persistent activity in dorsal prefrontal regions, like the frontal eye field (FEF), and the posterior parietal cortex (PPC) during the maintenance of positional information. This observation, however, does not answer what is actually being remembered or coded for by this activity (Curtis and D’Esposito 2003a). In a series of studies our aim has been to gain insight into the type of information coded by this activity. By manipulating the sensory and motor demands of the working memory task, we have been able to modulate the FEF and PPC delay-period activity. We’ve found evidence that retrospective sensory coding of space may be more prominent in the PPC, while prospective motor coding of space may be more prominent in the FEF (Curtis 2006; Curtis and D’Esposito 2006; Curtis et al. 2004). During a memory delay, one can look back to a past event, a retrospective code, or can look forward to a future event, a prospective code, in order to link events that are separated in time but are contingent upon one another. Both coding schemes are likely mechanisms of working memory and provide important clues to different contributions of the frontal and parietal cortices.

Recently, we directly tested the hypothesis that the maintenance of a prospective oculomotor plan is an important mechanism by which we maintain space (Curtis and Connolly 2008). We used an oculomotor deferred saccade task, in which the sensory cue was continuously present throughout the delay interval, rather than merely being transiently flashed prior to the delay interval. This paradigm eliminated the memory component (i.e., the need to remember the location of the saccade target) and placed the emphasis squarely upon oculomotor planning. We found that BOLD signals persisted in the frontal and parietal cortex throughout the delay interval even when working memory was not required. Therefore, the delay period activity that is often interpreted as the signature of working memory maintenance may in fact rely on mechanisms related to prospective motor planning to bridge the temporal gap between a stimulus and its contingent response.

We have also shown that these neural signals during memory delay cannot solely reflect oculomotor plans. For example, we find persistent neural activity in the frontal cortex during trials in which the forthcoming memory-guided response is not known until after the delay and therefore cannot be planned (Curtis and D’Esposito 2006; Curtis et al. 2004; Srimal and Curtis 2008). In an even more dramatic demonstration, we have recently found that activity in the frontal lobe persists when subjects are maintaining an auditory-cued location that is behind the subject’s head, a location that cannot be acquired with an eye-movement (Tark and Curtis 2007; 2008). These exciting new data not only call into question whether these signals are oculomotor in nature but they open up the possibility that they could reflect spatial representations that are not in eye-centered coordinates. Several members of the lab are currently conducting several follow-up studies of subjects localizing and maintaining auditory-cued space.

Common mechanism for spatial working memory, attention, and oculomotor intention

Spatial working memory maintenance may be mediated through sustained covert attention directed to the cued location (Awh et al. 2000; Postle et al. 2004). Similarly, spatial attention appears to be strongly coupled with the planning of an eye movement to the attended location (Awh et al. 2006). As discussed above, we have found evidence that persistent activity in the frontal lobe during a working memory delay period could represent 1) activation of a working memory representation of the stimulus’s position, 2) covert attention directed to the cued location, or 3) a planned saccade to the cued location. We conducted a series of studies that directly tested the long-standing question of whether the neural mechanisms that support each of these processes are shared. We scanned the same subjects in separate fMRI sessions while they 1) remembered the location of a briefly presented cue, 2) covertly attended to a cued stimulus to discern a slight change in it’s contrast, and 3) planned a saccade to the cue’s location or mirrored location. If these three spatial processes depend on a common mechanism they should activate at least some of the same brain areas. We found two frontal regions, one that is the likely human homolog of the monkey FEF, and one parietal region, the likely homolog of monkey area LIP. In Figure 2, we plot the independent and overlapping activation of each of the three processes color keyed by the annulus (note that white denotes the conjunction of memory, attention, and intention). That is the same exact cortical area was active during spatial working memory, spatial attention, and motor intention. Detailed analyses of the time series from the superior dorsolateral frontal area, the likely FEF, demonstrated that the BOLD signal in this area persisted during the maintenance of the position.
in working memory, during the maintenance of covert attention, and during the maintenance of an oculomotor intention (Figure 3). Also, we were able to show that during each of these processes there is a spatial bias; there is greater activation in the hemisphere opposite the location of the memory, attentional focus, and planned movement.

Figure 2. Persistent activation during the maintenance of working memory, attention, and/or intention. Each condition is coded by the color wheel on the right. We identified two frontal areas and one parietal area that showed persistent activity in all three conditions (white = common overlap; circled with black dashed lines).

Figure 3. BOLD time courses illustrating persistent neural activity with a contralateral bias in frontal cortex during the maintenance of working memory, attention, and intention.

Together, these data suggest that these frontal and parietal areas house a mechanism that is common among spatial working memory, spatial attention, motor intention. It may be the co-recruitment of these areas that lead to interference when two of these processes are required simultaneously in dual task behavioral studies. We are both surprised and excited at the degree of overlap in the pattern of activation across these tasks. It could have been equally plausible that slightly different areas of frontal and parietal cortex could support each of the functions. This is the first demonstration of such a remarkable overlap in activation related to spatial memory, attention, and intention (Curtis et al. 2008). This has forced us to rethink what types of computations are performed in these areas. For instance, we have argued that the human FEF does not simply compute the metrics for eye movement planning, but it plays a larger role in spatial cognition (Curtis 2006; Curtis and Connolly 2008; Ikkai and Curtis In Press; Srimal and Curtis 2008). For instance, persistent FEF activity may represent a prioritized attentional map of space, rather than the metrics for saccades. In order to test this, we have begun to map the spatial topography of the frontal and parietal cortex using phase-based retinotopic mapping procedures adapted for higher-level cognition for which the frontal cortex may be responsible. Our preliminary data are encouraging as we are finding topographic organization that maps on to the areas where we found common activation during memory, attention, and intention (Figure 4).

Effects of incentives on working memory

Although neural activity correlates with the expectation of reward in a variety of cortical and subcortical areas, such observations do not necessarily implicate these areas in the direct modulation of behavior based on reward. For instance, increased activity could simply reflect the greater effort that one is willing to exert in order to obtain the greater reward. Recently, using event-related fMRI, Mauricio Delgado and I imaged the human brain performing a spatial delayed-response task, while we independently manipulated both reward incentive and effort (Curtis et al. 2006; 2007). To manipulate incentive, we told subjects at the beginning of each trial how much money (5¢ vs. $5) could be gained or lost depending on their performance on that trial. At the same time, to manipulate effort, we told subjects how difficult the current trial was going to be (easy vs. hard). We controlled difficulty by adjusting the precision necessary to discriminate the spatial memoranda from a probe stimulus presented after the delay. A psychophysical staircase procedure was used to dynamically adjust difficulty to arrive at 85% and 60% accuracy for
the easy and hard conditions, respectively, for each subject. Behaviorally, reaction time, pupil size, and subjective ratings indicate that our manipulations of incentive and effort were successful. Neurally, classic oculomotor cortical areas showed strong effects of effort independent of the magnitude of incentive. Moreover, both the striatum and prefrontal cortex showed strong effects of reward incentive independent of effort level. These results suggest that effort and incentive may depend on distinct cortical and subcortical structures whose interaction promotes the attainment of desired goals.

**Homology between human and monkey - Translational research**

In these studies of spatial working memory, we have used memory-guided saccade tasks that are identical to those that have been used in monkey electrophysiological investigations (e.g., (Bruce and Goldberg 1985; Funahashi et al. 1989). This allowed us to use published electrophysiological data to aid in and strengthen the interpretations of our fMRI data. Specifically, we have been able to use the monkey electrophysiology data to argue that the blood oxygen level dependent (BOLD) signals in the human FEF arise from increases in neuronal spike rate during the memory delay. We have discovered several homologies between the patterns of BOLD and spike data. For example, just like that shown in monkey electrophysiological studies, we’ve shown that BOLD signals in the human FEF 1) persists above baseline for the duration of the delay (Curtis and D’Esposito 2006; Curtis et al. 2004; Srimal and Curtis 2008), 2) scales with the length of the memory delay (Srimal and Curtis 2008), 3) is spatially selective (Curtis and D’Esposito 2006; Srimal and Curtis 2008), and 4) correlates with the accuracy of working memory performance (Curtis et al. 2004). These findings provide an important confirmation for our assumption that we can use electrophysiological data to inform and constrain our interpretations of fMRI data. Moreover, the homology not only increases the inferential power of our studies, but it also provides important and needed translational data. We have tested highly influential animal models of human cognition in humans, which, although often overlooked, is needed before the full significance of research in another species can be realized. Because of the significance of our lab’s translational work, we remain in regular and close contact with several monkey electrophysiology investigators.

**Control of Action**

**Inhibitory control**

All animals are endowed with the capability of motor behavior. With that endowment they are faced with the continuous responsibility of selecting certain courses of action over others in order to ascertain their goals. A distinguishing feature of the higher animal species, like primates, is their exceptional ability to voluntarily control their actions. Voluntary control is necessary when an optimal motor response is uncertain or when a competing motor response must be overcome. A special case of voluntary control, or the more general term “executive” or “cognitive” control, is the ability to inhibit an unwanted action. Successfully withholding an over-learned, prepotent, or planned motor response is a critical demonstration of inhibitory control. Indeed, the ecological validity of such a construct is high and we can all think of a multitude of instances when we have had to inhibit our behavior. In social situations, our gaze at any given instant communicates to others information about our internal thoughts. For example, you might find it prudent to inhibit your glances towards an attractive person sitting at an adjacent table if you are dining with your partner.

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 and Carpenter 1999; Logan et al. 1984). Which process first reaches a critical threshold, or finish line, determines whether the planned response is generated or not. The presaccadic growth of activity in monkey 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). We were the first to demonstrate that during a stop-signal task, 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 et al. 2005). The increased activation likely reflects the co-activation of saccade and fixation neurons on STOP trials.

Similar changes in FEF saccade and fixation neural activity can be seen when an animal prepares to inhibit an unwanted action, for instance a saccade to a visually salient target. Prior to 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 (Munoz and Everling 2004). We have demonstrated in humans that FEF activity increases prior to antisaccade trials compared to prosaccade trials (Curtis and Connolly 2008; Curtis and D’Esposito 2003b). The increase is presumably due to the co-activation of saccade and fixation neurons in the FEF prior to antisaccade trials. 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 (Curtis and D’Esposito In Press). An important implication of these data is that the inhibition of an unwanted action emerges or is the consequence of the competition between different potential responses. Therefore, inhibitory control like voluntary control more generally may be best modeled as the process by which we select the best response among all competing responses, including not responding at all. At least at the level of premotor structures, a mechanism specialized for inhibiting actions, per se, does not seem necessary for the behavioral expression of inhibiting an unwanted action.

**Saccade adaptation**

We have also begun a new line of research involving the neural mechanisms of unconscious, non-voluntary forms of motor control and learning. Within the oculomotor system, the motor programs issued given the position of the visual target on the retina remain accurate in the face of fatigue, injury and aging. Such plasticity emerges through motor learning mechanisms that continually adapt the system to new sensorimotor transformations. We recently tested the hypothesis that saccade gains adapt to minimize error between the visual target and the saccade endpoint of every saccade we make even when the errors on sequential saccades are not directionally consistent (Srimal and Curtis 2006; Srimal et al. In Press). We utilized a state-space model that estimated the degree to which saccade gains were modified by the magnitude and direction of errors made on the previous trial. We assumed that an inverse dynamics model computes the motor command necessary to generate the desired saccade. An efference copy of the motor command is sent to a forward model, which predicts the sensory error given the current state of the system and the perturbation to the system. This error is weighted by a learning parameter to form the teaching signal that trains the inverse dynamics model to produce an updated motor command. Importantly, to show that learning did not depend on the accumulation of directionally consistent errors, we fit the model to saccades made to targets that were displaced in a random direction during the saccade, thereby inducing
errors whose directions were not sequentially consistent. Saccade gains clearly adapted on a trial-by-trial basis despite that the perturbations were random, and the average amount of learning per trial was of similar magnitude as that found in a constant displacement of the target. We concluded that the oculomotor system adapts to random perturbations in motor control via a mechanism that is rapid, obligatory, and does not require conscious awareness. Moreover, these features fit well within emerging theories of motor control composed of dynamic internal models used to compute and anticipate the sensory consequences of motor actions. Currently we are conducting a series of fMRI studies that use the trial-by-trial model parameters of learning to predict BOLD signal changes in the brain.