this hypothesis were obtained in mice deficient in parallel fiber LTD, which can learn to blink to a tone following classical conditioning but exhibit inaccurate blink timing (De Zeeuw and Yeo, 2005). The two studies discussed here provide the first firm physiological evidence for the predicted forms of plasticity at the mossy fiber to deep nuclear synapse. It is intriguing to speculate that the LTP described by Pugh and Raman could participate in acquisition of eyeblink conditioning, while the LTD described by Zhang and Linden may play a role in extinction. Other forms of cerebellum-dependent learning, including adaptation of the vestibulo-ocular reflex or of reaching movements, are likely to rely on similar forms of plasticity. Because so much is known about the downstream effects of deep nucleus neuronal activity, the consequences of experimental manipulations that specifically enhance or abolish each type of synaptic plasticity can be assessed in behaving animals, providing one of the rare opportunities to forge a clear link between physiological plasticity and behavioral learning in vertebrates.

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Progress in Understanding Spatial Coordinate Systems in the Primate Brain

A new study in this issue of *Neuron* shows that when monkeys reach to a visual target, neurons in the dorsal premotor cortex compare the location of the target, the hand, and the point of visual fixation. The neurons therefore encode space through a combination of eye-centered and hand-centered coordinates.

We act on the world by reaching, grasping, manipulating, looking, avoiding, and performing hundreds of other actions on the objects around us. These behaviors depend on computing the relative spatial locations of objects and body parts. How does the brain coordinate spatially accurate behavior? The dorsal premotor cortex (PMd) of the monkey brain, and more specifically the caudal division of PMd (PMdc; see Figure 1), is densely connected to a network of motor structures, including the spinal cord, and is involved in the control of reaching. In a new study, Pesaran et al. (2006) show in this issue of *Neuron* that PMdc may guide the arm by means of a simultaneous comparison of hand location, eye location, and target location. Here I outline some of the previous experimental steps in understanding the representation of space in parietal and frontal cortical areas and discuss how the present finding significantly extends this line of research.

Retinal Receptive Fields Modulated by Extraretinal Factors

One of the first accounts of how neurons represent space was proposed by Andersen et al. (1985). They described visually responsive neurons in area 7a of the posterior parietal lobe of monkeys. Like classical visual neurons at most stages of the visual system, each neuron in area 7a had a visual receptive field on the retina. The magnitude of the response of a 7a neuron, however, was modulated by the angle of the eyes in the orbit. When the eyes were angled one direction, the neuron might become relatively unresponsive. When the eyes were angled another direction, the neuron might become highly responsive to visual stimuli. The two pieces of information that influenced the neurons, the location of the stimulus on the retina and the location of the eyes in the orbit, could in principle provide the location of an object with respect to the head.

Further work by Andersen and colleagues (Brotchie et al., 1995; Snyder et al., 1998) revealed that not only the angle of the eyes in the orbit, but the angle of the head on the trunk, and vestibular information about the position of the head in the world, also modulated the responsiveness or the "gain" of neurons in posterior parietal areas. From this work, a general model of spatial coding emerged. In this model, neurons have receptive fields on the retina, explicitly encoding space in eye-centered coordinates. The response gain of the neurons, however, is modulated by additional spatial factors. As a result, the pattern of activity across a population of neurons carries information about the location of a visual stimulus with respect to the eye, the head, the trunk, and the external world.
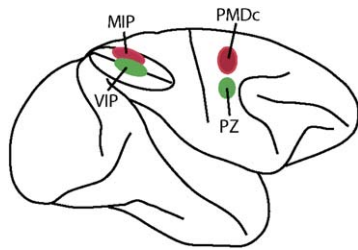
Figure 1. Side View of Macaque Monkey Brain Showing Approximate Location of Four Cortical Areas that Code Visual Space in Different Ways

The intraparietal sulcus is opened to show the buried cortex. PMDc, caudal dorsal premotor cortex. Neurons in PMDc encode reach targets in a complex combination of eye- and hand-centered coordinates. Stimulation here tends to evoke reaching-like projecting of the arm and opening of the hand. MIP, medial intraparietal area. Neurons here encode reach targets in eye-centered coordinates. MIP and PMDc are densely interconnected. Electrical stimulation has not been extensively tested in MIP. PZ, polysensory zone within the ventral premotor cortex. Neurons here have tactile receptive fields and visual receptive fields anchored to the body surface in "body-part-centered" coordinates. Stimulation here tends to evoke defensive or protective movements. VIP, ventral intraparietal area. Neurons here have tactile receptive fields and visual receptive fields in the space adjacent to the tactile receptive fields. The visual receptive fields encode visual stimuli in a combination of eye- and body-centered coordinates. Stimulation here tends to evoke defensive-like movements. VIP and PZ are densely interconnected.

The modulation of response gain by extraretinal spatial variables was found to be ubiquitous among parietal and frontal areas and is now a well-established component of spatial coding. However, this model of retinal receptive fields modulated by extraretinal spatial variables turned out to be an incomplete description of spatial coding in the brain. Not all neurons involved in spatial coding have visual receptive fields fixed to the retina. Some neurons appeared to encode visual space by means of receptive fields fixed to other reference points.

Receptive Fields Anchored to Specific Body Parts
In the ventral premotor cortex in the polysensory zone (PZ; see Figure 1), a subset of neurons was found to respond to tactile stimuli on the face and to visual stimuli in the space near the face (Rizzolatti et al., 1981). The response magnitude of these neurons was modulated by eye position, like the neurons described by Andersen et al. (1985) in area 7a. However, the receptive fields of the bimodal, visual-tactile cells were not fixed to the retina. Instead they were anchored to the tactile receptive field on the body surface (Graziano and Gross, 1998). A bimodal neuron with its tactile receptive field on the face behaved as if its visual receptive field were an inflated balloon glued to the side of the face. When the eyes moved, the response magnitude of the neuron might change, but the location of the receptive field remained unaffected. When the head rotated, the receptive field moved with it. Head-centered receptive fields were also described in restricted regions of the parietal lobe (Duhamel et al., 1997).

Some of the bimodal neurons in the premotor cortex had a tactile receptive field on the arm and a visual receptive field apparently glued to the surface of the arm (Graziano and Gross, 1998). The response magnitude of the neuron might be modulated by rotations of the eyes or head, but the spatial location of the receptive field remained fixed to the arm. When the arm moved, the receptive field moved with it.

This finding of visual receptive fields deep in the motor system that are anchored to different parts of the body surface led to the suggestion that near the output stage, visual space must be constructed many times over, attached to different body parts for different purposes (Graziano and Gross, 1998). In this hypothesis, the visual guidance of each body part requires a visual coordinate frame anchored to that body part, in order to encode the locations of objects with respect to the body part. For example, guidance of head movements requires head-centered visual receptive fields and guidance of hand movements requires hand-centered visual receptive fields.

The body-part-centered hypothesis was proposed as a general solution to the problem of visuomotor integration. It now appears to play a much less general role. First, recent evidence suggests that the bimodal neurons in ventral premotor cortex are relatively more specialized for withdrawal than for reaching (Graziano and Cooke, 2006). Second, the body-part-centered hypothesis predicts that neurons involved in reaching should encode the location of the target relative to the hand. Yet studies of reach-related neurons consistently found a spatial code linked to the eyes instead of the hand.

Eye-Centered Coordinates for Reaching
Batista et al. (1999) examined neurons in the medial intraparietal area (MIP; see Figure 1). Each neuron had a reach field: when the monkey prepared to reach for a target within the reach field, the neuron would respond. The reach fields, however, were not anchored to the hand, but to the eye. Why should neurons known to be involved in reaching have receptive fields in eye-centered coordinates? Two mutually consistent interpretations were suggested. One is that the eye-centered coordinates are the common currency of the parietal lobe, allowing for easy transfer of spatial information from one brain region to another. The second interpretation is that the visual guidance of reaching does ultimately require hand-centered coordinates, but the hand-centered receptive fields are not constructed until a later stage in the processing, perhaps within premotor or motor cortex.

Multiple Coordinate Frames Represented within the Dorsal Premotor Cortex
The PMDc receives a direct projection from MIP and projects to other motor structures, including the primary motor cortex and the spinal cord. Neurons in PMDc are believed to be involved specifically in the control of reaching. Do these neurons encode the location of reach targets in a hand-centered coordinate system?

In the experiment by Pesaran et al. (2006), monkeys reached to a set of targets while the starting hand and eye positions were varied. Each neuron responded when the monkey prepared to reach into a restricted region of space, the neuron's reach field. The primary finding was that the reach fields were not anchored to the eye, nor were they anchored to the hand. Indeed, these reach fields were not strictly anchored to one reference point. Rather, the firing rate of the neurons was a function of the spatial relationship between the target and the eye, the target and the hand, and the eye and the hand.

This elegant study shows that there is no simple answer to the coordinate frame question. PMDc neurons

do not appear to encode reach targets in a hand-centered coordinate frame or in an eye-centered one. A different conception may be necessary, in which there is no single spatial coordinate system. Rather, a diverse set of spatial information that is normally used during the act of reaching is multiplexed in the response profile of these neurons. To the extent that hand-centered spatial information is required, it is present. But eye-centered information is also present, perhaps because reaching normally involves a close interaction between the hand and the eye.

Different Spatial Representations Optimized for Different Types of Actions?

Reaching to a target is only one type of spatially guided action. Monkeys and humans perform other actions, such as manipulating objects that are already grasped, bringing objects to the mouth, or avoiding contact with potentially dangerous objects. Each of these actions has its own idiosyncratic properties and requires its own mixture of spatial information. For example, consider the problem of avoiding an object, such as a bee, flying toward the body surface. The spatial relationship between the bee and the projected point of contact on the body is of paramount importance. In this case, hand-centered coordinates and eye-centered coordinates may be less important than side-of-the-neck-centered coordinates, if that is where the bee is headed. The standard defensive reaction might involve a rapid lifting of the shoulder, ducking of the head, and withdrawal of the body. The sensorimotor problem here is quite different from the problem of reaching the hand to a target.

As described above, neurons in a polysensory zone in the ventral premotor cortex have tactile receptive fields typically on the upper body and visual receptive fields apparently anchored to the body surface at the site of the tactile receptive field. Our initial hypothesis regarding these neurons was that they might contribute to the general sensory guidance of movement (Graziano and Gross, 1998). However, when we electrically stimulated these polysensory sites in cortex, we consistently evoked apparent defensive movements including ducking, withdrawing, lifting the shoulders, and lifting the arm as if to block a threat (Graziano and Cooke, 2006). Even under anesthesia, we evoked movements that appeared to defend the site of the tactile receptive field on the body. In contrast, stimulation in PMDc tended to evoke an opening of the hand and a projecting movement of the arm consistent with reaching.

The stimulation evidence suggests that different subregions of motor cortex may partially specialize in different categories of action. These subregions of cortex, therefore, may encode the space around the body in different ways, optimized for different types of action.

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Cognitive Control Signals in Visual Cortex: Flashes Meet Spotlights

At the intersection of two intensely belabored fields, primary visual cortex (V1) function and neural mechanisms of cognitive control, Jack et al. (in this issue of Neuron) report a neural signal that is neither related to stimulus representation nor spatial attention. Instead, this endogenous signal correlates with task structure and raises new questions.

Across several species, primary visual cortex (V1) is arguably the most heavily studied and best understood brain area. The investigation of its functional response properties was heralded by the seminal work of Hubel and Wiesel who were first in eliciting reliable and selective responses of single neurons to sensory stimuli. These stimulus-related response properties included retinotopic receptive fields and orientation selectivity and have appeared in every neuroscience textbook. Along these lines, V1 is still often thought of as a camera-like device that provides a somewhat distorted and fractured but fairly veridical representation of the retinal image. Yet its neurons seem to be involved in functions going beyond mere image representation.

This insight comes as no surprise if one considers the anatomical connectivity of V1 and realizes that retino-geniculo-cortical afferents provide only a fraction of its input (Casagrande and Kaas, 1994). Despite these anatomical clues, it has proven more difficult to evoke V1 responses by mechanisms other than sensory stimulation, as for instance by visual imagery or spatial attention, cognitive processes that are associated with strong activity changes elsewhere in the brain. Following initial sparse electrophysiological reports of attentional V1 activity modulation, significant progress came from functional magnetic resonance imaging (fMRI) studies that mapped activations during covert spatial attention to corresponding retinotopic representations of the attended visual field locations (reviewed in Posner and Gilbert, 1999).