be based on elevated activity of either excitatory or inhibitory neurons, as each represents an increase in cellular metabolism. Conversely, decreases in BOLD signals probably arise from regional decrements in excitatory or inhibitory neural activity, but this, too, has not been established. The hope is that by using electrode recordings in concert with fMRI in animals, it will be possible to determine the relationship between increases and decreases in the activity of excitatory and inhibitory neurons and changes in the BOLD signal. Obviously, this has important implications for our interpretation of the fMRI images obtained from the human brain.

Although it is true that the use of microelectrodes provides better spatial and temporal resolution than fMRI, there is a valuable place for fMRI in animals. The technique provides a global picture of brain activity that complements the microscopic view observed with an electrode (or even an array of electrodes). Many years of electrode studies imply that behavioral tasks are performed by the concerted activity of neurons spread across numerous cortical areas, and fMRI lets us see these distributed activity patterns. In addition to the inherent value of the fMRI images, they are an ideal tool for guiding investigations with electrodes into poorly understood aspects of perception and cognition. One cannot focus on the trees until the forest is first located. Where should one record with electrodes to learn about neural mechanisms underlying object recognition, shifts in attention or problem solving? Pioneering studies with fMRI could conceivably locate hotspots involved in such tasks and save years of hunting with microelectrodes.

The most exciting aspect of the fMRI work in the monkey is the lessons it may teach us about the function of the human brain. In the past decade, there has been an explosive increase in the use of fMRI in humans, and this technique, along with positron emission tomography (PET), has virtually defined the new field of cognitive neuroscience. Around the world, perceptual, cognitive and limited behavioral tasks are performed by humans laying inside magnets large enough to move cars, like mummies inside sarcophagi. This approach to studying the brain has already led to exciting results, suggesting that certain areas are preferentially activated in tasks involving object recognition, working memory and mental imagery, among others[13]. Yet, until there is a connection to research in experimental animals, our knowledge of the human brain will remain constrained by the limited resolution of the fMRI technique and its indirect relationship to neural activity. Now, with the advent of fMRI imaging in monkeys, parallel studies can be done in the two species and the results compared to identify brain regions that might subserve homologous functions (Fig. 1). Such comparison could facilitate huge advances because the results of vast amounts of animal research can be applied toward an understanding of the human brain. After all, this is why much of the primate research is done in the first place. We are a selfish species, and we want to understand our own brains and learn to remedy neurological disorders when they arise. How do we see and feel? How are memories formed and why do they fade? What circuitry is lost when a stroke causes a loss of coordination? With the development of fMRI in monkeys, we have a bridge between human studies and the large body of animal research, which we hope will lead us to answers for such questions. Thus, the small step backward in monkey research taken by Logothetis *et al.* may be a giant leap forward for understanding the human brain.

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Adjusting reaches: feedback in the posterior parietal cortex

Marco Iacoboni

Transcranial magnetic stimulation reveals that reaching movements are fully planned before movement onset but can be adjusted by feedback acting via the posterior parietal cortex.

As every toddler instinctively knows, reaching out for surrounding objects is central to controlling our environment. Two contrasting theories of motor control during the execution of visually guided movements propose that reaching movements are either planned before movement onset or generated in real-time while movement unfolds. Sudden changes in some aspects of the environment, however, can require dynamic adjustments after movement initiation, which must preserve the precision and timing of the originally planned action. These adjustments, which can occur without our awareness of target displacement[1], require some sort of feedback mechanism that monitors hand position in space and estimates errors. In this issue of *Nature Neuroscience* (pages 563–567), Desmurget and colleagues take advantage of the relatively new technique of transcranial magnetic stimulation (TMS) to demonstrate that reaching movements are fully planned before movement onset and that the posterior parietal cortex is critical for the feedback mechanism that allows us to adjust to sudden target displacements during the reaching movement.

The third important contribution of this study is in identifying the functional level at which this posterior parietal feedback mechanism acts to correct reaching to displaced visual targets. When we reach for an object,

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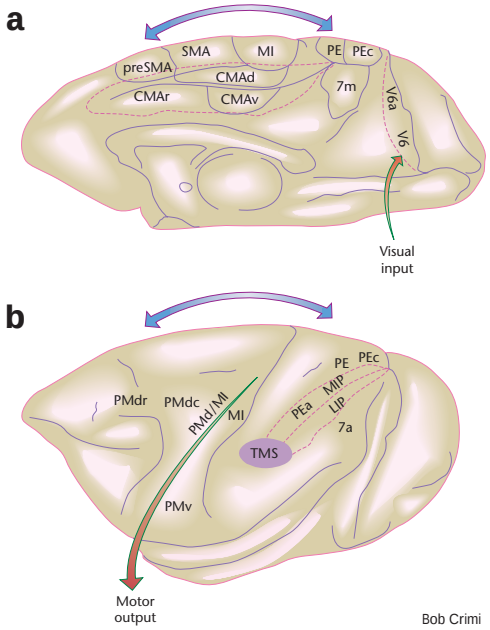

Fig. 1. Brain areas involved in reaching in monkeys. Arrow indicates reciprocal connections among parietal and premotor regions. (See ref. 4 for a detailed description of these connections.) Purple area shows the region roughly homologous to the site of TMS stimulation in the study by Desmurget and colleagues.

we have to convert visual information that is coded in frames of reference used by the visual system into the different frames of reference that are available to the body parts used to generate actions. The posterior parietal cortex, which receives strong inputs from cortical areas of sensory significance and sends strong outputs to cortical areas of motor significance, is in an ideal position to compute this reference frames conversion[2]. The study of Desmurget and colleagues demonstrates that the feedback mechanism that allows dynamic updating of reaching movements occurs at motor and not at visual or intermediate levels.

The authors used a simple and elegant experimental design. They asked normal subjects to 'look and point' to lights. In some trials, the original light was turned off during reaching, and a new light was presented in a new location. Because the change occurred during a saccade, when vision is attenuated, subjects were unaware of the displacement. In half of the trials, TMS was applied to the posterior parietal cortex to transiently disrupt its function. Reaching movements were inaccurate in trials with displaced targets when TMS was applied. In contrast, when the visual target remained in the original location, TMS did not disrupt the reaching movement. The lack of an effect of TMS during reaching to stationary targets shows that the effect is selective and suggests that movements are fully planned before movement onset. Two control stimulation sites confirmed that the effect was specific to posterior parietal cortex. When TMS was applied to a temporal area or to motor cortex (respectively relevant to vision and motor control), reaching for misplaced targets was not disrupted. It may seem surprising that reaching movements were not disrupted when TMS was applied to the motor cortex, but there is evidence that nonprimary motor areas connect directly with the spinal cord[3]. In principle, therefore, it is possible to bypass the primary motor cortex via direct corticospinal pathways originating from other cortical motor areas. Indeed, these regions belong to corticocortical networks that are involved in reaching and receive inputs from the posterior parietal cortex[4]. Finally, Desmurget and colleagues used a clever experimental manipulation; they asked their subjects to reach to the same location with the contralateral hand. When subjects switched the hand used for reaching, the previously observed inhibition of reaching adjustment by TMS disappeared. This suggests that the feedback mechanisms of the posterior parietal cortex affect the motor effectors of reaching.

As in most experiments providing exciting results, this study raises more questions than it solves. Most immediately, what is the role of other sources of information, such as auditory, tactile and proprioceptive, in the feedback mechanism controlled by the posterior parietal cortex? Functional neuroimaging indicates that areas in the human posterior parietal cortex equivalently code basic sensorimotor transforms for visual and auditory stimuli[5]. There is also psychophysical evidence that multisensory fusion occurs during reaching, perhaps to provide egocentric representations of space[6]. However, some premotor[7] and posterior parietal[8] neurons respond selectively to either auditory or visual stimuli. The role of different modalities in the feedback mechanism during reaching to nonstationary targets will require further investigation.

Another direct question raised by this paper[15] is how to define more precisely the contribution of the posterior parietal cortex and/or interconnected areas in the functional mechanism disrupted by TMS. Macroscopically, the posterior parietal cortex is divided in two main sectors, the inferior parietal lobule and the superior parietal lobule. Lesions in the superior parietal lobule are associated with optic ataxia, a classical disorder of reaching in human neuropsychology[1]. The posterior parietal cortex in general and the superior parietal lobule in particular, however, are composed of a variety of areas that belong to dense corticocortical networks including mainly prefrontal and premotor areas[2,9] (Fig. 1). In nonhuman primates, neurophysiological studies show that the superior parietal lobule is indeed involved in processing visual information necessary for reaching[10]. The picture that emerges from these studies is that reach-related neurons in monkey parietofrontal networks are organized according to sensory-to-motor gradients. There is a ventrodorsal sensory-to-motor gradient in the posterior parietal cortex and a corresponding rostrocaudal sensory-to-motor gradient in the dorsal premotor cortex. Within these cortical networks, there is no

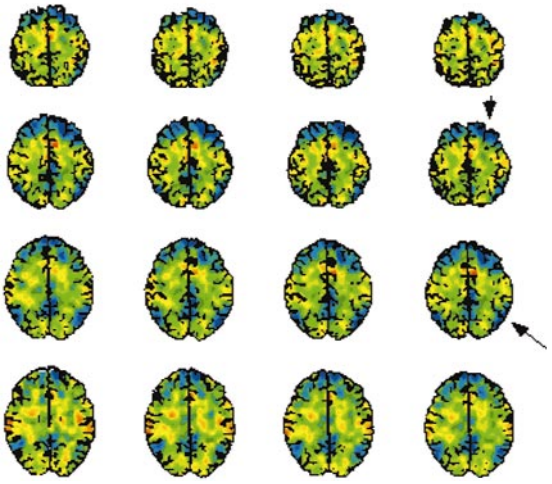

Fig. 2. Patterns of frontoparietal functional connectivity in the human brain during sensorimotor transforms. The frontal rostrocaudal sensory-to-motor gradient and the corresponding parietal ventrodorsal sensory-to-motor gradient observed in the monkey are discernible in these PET maps of functional connectivity in normal subjects. The gradients are color coded from blue (low) to yellow to green (high). Arrows show the frontal and parietal gradients in two different planes. In these sixteen axial planes, the cortical sulci are outlined in black.

clearcut boundary between the 'sensory' and the 'motor' region, and the properties of the neurons change gradually along the gradient. Also, parietal and frontal regions with similar properties (more 'sensory' or more 'motor') are reciprocally connected. Taken together, these features of the parietofrontal networks involved in reaching suggest functional overlap in parietal and frontal regions that may favor combinatorial and recursive processing[4], which may be especially useful in feedback mechanisms.

Functional neuroimaging studies of the human brain are in support of this view. In a recent PET study, subjects attempted to reach to visual targets while wearing prisms producing visual displacement. After initial misreaches, subjects adapted quickly. The PET data showed that activity in the posterior parietal cortex correlated with the adaptation process[11]. Human brain mapping during basic sensorimotor transforms[12] shows spatial modes of functional connectivity (Fig. 2) that resemble the sensory-to-motor gradients observed in the monkey. Thus, even though the posterior parietal cortex is clearly involved in feedback for reaching to nonstationary targets, we cannot rule out the possibility that dorsal premotor regions relevant to reaching movements may be involved in feedback mechanisms as well. The use of TMS applied over cortical regions anatomically and functionally connected to the posterior parietal cortex will address this issue.

Recently, TMS has also been used in functional neuroimaging settings to explore aspects of functional connectivity in the human cerebral cortex[13]. Although Desmurget and colleagues used TMS to interfere with normal activity, it can also evoke activity that is propagated to connected brain regions. Thus, TMS coupled with functional neuroimaging techniques may provide a better definition of the corticocortical networks controlling feedback mechanisms during reaching. It may also help in disentangling the relative contribution of frontal and parietal regions in the functional aspects of reaching and its feedback mechanisms. Finally, at a functional level, there are several questions that will be probably addressed in the near future with experimental designs similar to the one used by Desmurget and collaborators. For instance, visual distractors affect arm trajectory during reaching[14]. Can this effect be disrupted by TMS applied over the posterior parietal cortex?

Finally, a central role of the posterior parietal cortex in feedback mechanisms during motor behavior might provide an explanation for empirical observations in stroke patients. When motor recovery is monitored over time in a group of stroke patients with hemispheric lesions in various locations, recovery of function is reduced in patients with parietal lesions, compared to patients with lesions in other locations[15]. If the posterior parietal cortex is critical for feedback mechanisms in motor behavior, then rehabilitation and even spontaneous recovery should be more difficult after lesions of the posterior parietal cortex, as patients do not receive normal feedback on the results of their actions. A better understanding of motor control, both in its functional, computational aspect and in the neural substrates of these computational processes, might help in delineating more effective and more diversified rehabilitation strategies in neurological patients with motor and sensorimotor disorders.

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Quantal GABA release: noise or not?

Kevin J. Staley

The new finding that seizures can change the probability of action-potential-independent transmitter release in rats suggests that these events may carry synaptic information.

Since the first descriptions of quantal release of actetylcholine at the neuromuscular junction[1], it has been clear that neurotransmitter release is a stochastic process. There is a substantial probability of failure (an action potential arrives at the nerve terminal but no transmitter is released), as well as a corresponding probability of transmitter release without a presynaptic action potential[2]. Should we consider these rogue quanta and failures to be noise or information? The answer depends on the nature of synaptic transmission. The finding of Bernard and colleagues, in this issue of *Nature Neuroscience* (499–500), that the probability of action-potential-independent transmitter release is decreased in an animal model of epilepsy supports the idea that these events may contain information.

The increase in release probability following an action potential results from calcium influx via voltage-dependent calcium channels[3]. Because calcium's interaction with the vesicle release machinery varies with the fourth power of the local calcium concentration, even a relatively small calcium influx can cause a large increase in release probability. Without an action potential, the calcium concentration in the terminal is so low that no more than one transmitter vesicle is likely to be released at a time. The release of these single vesicles generates miniature postsynaptic cur-

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