

Pursuing commitments

Michael N. Shadlen

Two new studies elevate cortical microstimulation from production of surrogate sensory or motor signals to cognitive control signals, confirming suspicions that brain areas that specify movements may also be involved in cognitive processes such as attention and selection.

Faced with a number of possibilities, it is often a good idea to delay making a commitment in order to watch how things play out. Although this strategy forces us to entertain several possibilities at once, it helps us to optimize our decisions by taking advantage of any new information that may arrive. It also postpones costly computations that may lack relevance until we are ready to act. Our sensory systems support this juggling act by dividing attention and assigning probabilities to several possible interpretations of a scene until queried. Our motor systems can delay calculations involving the state of our body machinery (for instance, position) until just moments before movement begins¹. In general, controlling the conversion from several possibilities to a single commitment may be thought of as a cognitive module that incorporates shifts of attention, decision-making and movement selection. Neuroscientists are beginning to expose the mechanisms that underlie such cognitive steps^{2–5}. Progress in this budding field of cognitive neuroscience has been catapulted forward by two recent experiments^{6,7} that demonstrate for the first time a causal relation between neural activity and cognitive state.

Both studies used electrical microstimulation of cortical neurons to cause a cognitive event in monkeys trained to perform complex sensorimotor tasks. In a study by Moore and Fallah⁶, microstimulation caused monkeys to shift their state of attention. And in this issue of *Nature Neuroscience*, Gardner and Lisberger used microstimulation to bring about a commitment to an interpretation of visual motion⁷. Both experiments involve stimulation of a brain

structure that is known to be involved in moving the eyes—yet both caused changes in mental states more mysterious than movement.

In Moore and Fallah's study⁶ (Fig. 1), monkeys were trained to detect a subtle change in one visual target among distractors. The task is easier if attention can be drawn to the appropriate part of the visual field. Normally this is accomplished by cueing the subject to the relevant stimulus—this works for both humans and monkeys. Reasoning that we often look where we attend, Moore and Fallah stimulated neurons in the frontal eye field (FEF) that are known to command rapid saccadic eye movements. The authors knew that if they stimulated with enough current, they would cause the eyes to move to the region of the visual field labeled 'motor field' in Fig. 1. However, in their attention experiment, they decreased the stimulation current to less than the amount that would actually cause an eye movement. Instead of producing a movement to the motor field, the stimulation caused the monkey to maintain attention at this location. The monkey detected the target efficiently, as if attention were drawn to the target in the motor field and away from the distractors. It thus appears that the neural circuitry that causes a movement to a location can direct the rest of the brain to focus its sensory machinery on that spot.

In the study by Gardner and Lisberger⁷, stimulation caused the monkey to stop hedging its bets and to commit to one possibility. Their strategy is founded on previous research that shows how primates shift their gaze to moving objects. When we see an object moving in our visual field, we do two things. We make a fast orienting eye movement known as a saccade, and we track the moving object by moving the eyes in smooth pursuit. To do this accurately, we need to know where the object is and how fast it is moving. That way, when we fix upon it, we do not end up where it was before we started the sac-

cadic eye movement, and we do not immediately lose the object as it moves away from the new position of our gaze. For this to work, the brain must calculate the object's motion before it starts the saccadic eye movement, allowing it to begin the pursuit movement as soon as the eyes land on the target without further calculation.

But what if there is more than one moving object in the visual field? In this case, the brain hedges its bets by analyzing the motion of each object (Fig. 2). It turns out that we can see evidence for this analysis before commitment by contriving a situation in which the pursuit eye movement begins before the saccadic eye movement. If two objects are moving in different directions, the brain calculates two velocities and moves the eyes

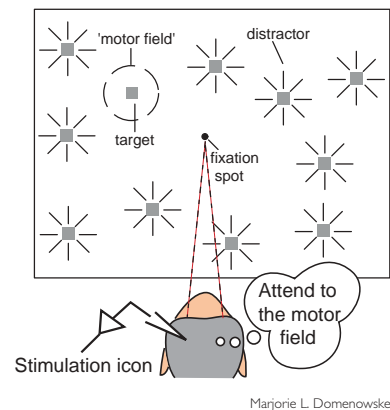
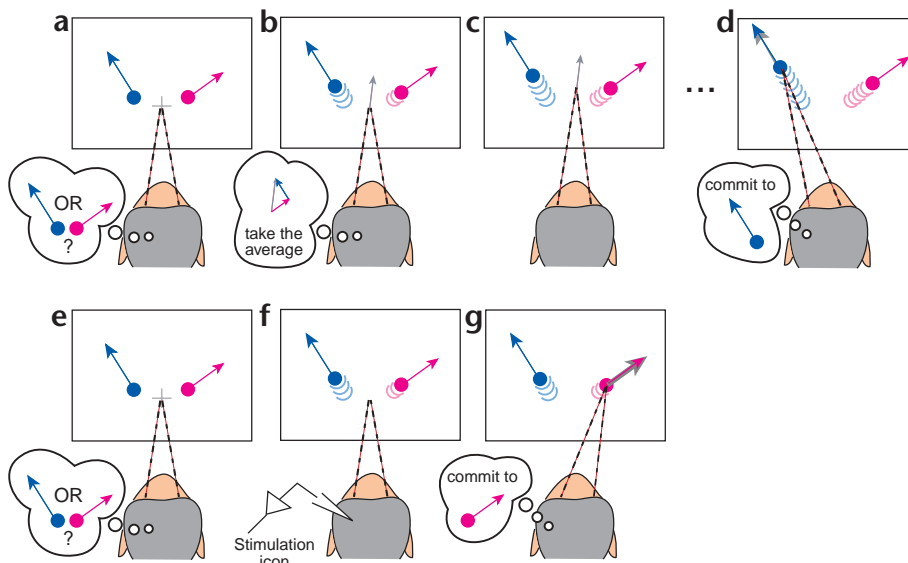


Fig. 1. In Moore and Fallah's experiment⁶, the monkey was rewarded for detecting a change in the intensity of the target. Sensitivity improves if attention is directed to the target and away from the distractors. Moore and Fallah used microstimulation of neurons in the frontal eye field to direct the monkey's attention to the target. At high currents, microstimulation causes a rapid eye movement to the 'motor field' of the stimulated neurons. Moore and Fallah found that stimulation with lower current intensity failed to move the eyes but instead caused the monkey to direct attention to the target in the motor field. Adapted from ref. 6.

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Fig. 2. In Gardner and Lisberger's experiment⁷, the monkey was trained to track moving targets. If two targets are moving at velocities shown by the colored arrows (a), the monkey initially tracks both targets with a smooth eye movement at an intermediate velocity, which is the vector average of the two motions (gray arrow in b and c). At some point, the monkey makes a saccadic eye movement to one of the targets. Once the monkey commits to this target, the smooth pursuit eye movement immediately acquires the velocity for the chosen target (gray arrow in d). On some trials, instead of waiting for the monkey to commit, Gardner and Lisberger evoked a saccadic eye movement by stimulating neurons in the frontal eye field (e–g). The experiment was designed so that the evoked eye movement landed on one of the moving targets. The pursuit eye movement immediately acquired the velocity of this moving target, even though the evoked movement occurred before the monkey would normally commit to one of the targets (gray arrow in g). Because of delays in visual processing, it is known that this pursuit velocity is calculated by the visual system before the saccadic eye movement lands on the target. This means that the stimulation of a saccadic eye movement caused the pursuit tracking system to commit to one target.

along a direction and at a speed that is intermediate to each: it chooses the vector average⁸ (Fig. 2b and c). This velocity may be the best estimate for both objects, but it is correct for neither. This state of affairs can go on for up to 100 milliseconds or so, but once the brain is committed to fixing upon one of the objects, a saccadic eye movement is made and the brain gives up on its intermediate solution. There are two types of evidence for this commitment. First, the saccadic eye movement is accurate: it accounts for the motion of its target object, not the intermediate value. Second, when the gaze lands on target, the eyes immediately begin smooth pursuit at the correct speed and direction⁹. Thus, upon commitment, the pursuit system abandons the vector average velocity and instead adopts the velocity of the chosen object.

Gardner and Lisberger wondered whether the brain circuitry involved in generating the saccadic eye movement would also cause the pursuit system to settle on the one appropriate velocity signal. In short, they asked if the neurons that cause us to grasp with our gaze also cause us to commit. They tested this

idea by presenting two different motions to the monkey and then stimulating the FEF to cause an eye movement (Fig. 2e and f). Gardner and Lisberger knew ahead of time the location of the movement field of the neurons they were about to stimulate. They cleverly set up the moving targets so that stimulation would cause a saccadic eye movement to one of them. Importantly, they stimulated the eye movement before the monkey would normally commit to one of the targets, that is, when the brain would normally hedge its bets and use the vector average velocity for pursuit. They could then ask: when this premature eye movement reaches its target, does the tracking that ensues immediately thereafter adopt the intermediate velocity, or has the pursuit system been forced to commit to one velocity?

They observed the latter: stimulating the FEF caused not only an eye movement but also a commitment to tracking the target at that location. The finding that the pursuit system can be jolted into one velocity interpretation suggests that it had access to the velocity of each object all along and simply chose to adopt the intermediate value.

This was not a foregone conclusion. In principle, the intermediate velocity or vector average could have resulted from the visual system failing to segment the two moving objects and instead computing the average motion of the ensemble. That does not seem to be the case, because stimulation caused the pursuit system to adopt the velocity of one object without further calculation. This means that the brain has the individual representations of velocity for each object—it just chooses to ignore them until the moment of commitment.

Gardner and Lisberger conclude that the brain circuitry that is responsible for making fast orienting eye movements causes the pursuit tracking system to commit to an interpretation of motion. That is the nuts-and-bolts lesson, but there is a deeper principle here that is exposed by examining the link to Moore and Fallah's result. In both experiments, neurons that are known to command a shift in gaze also command other neural systems to commit resources to that location. As Moore and Fallah reason, we attend to the things we look at. It makes sense for the brain circuitry that says "move the eyes over there" to also



say to the rest of the brain that “over there” is the location that matters. If this is correct, then the FEF might cause a variety of brain circuits to focus machinery on the location of interest. In principle, it ought to be possible to study the mechanism of attention/commitment by stimulating the FEF and recording from neurons involved in visual processing. Experiments using this approach will be presented at the next meeting of the Society for Neuroscience (T. Moore & K. M. Armstrong, *Soc. Neurosci Abstr.* 28, 418.6, 2002).

These two studies take microstimulation to a new level: the stimulation of change of cognitive state. Microstimulation of the brain has been used as a surrogate signal to show that neurons control body parts or represent the sensory quantities that investigators deduced from recording experiments. It has also been used to cause an action prematurely to reveal intermediate states of neural computations involved in motor planning^{1,10}, decision making¹¹ and shifts in attention¹². Gardner and Lisberger exploited both of these strategies. By causing an eye movement prematurely, they show that the brain actually represents the motion of each object even when the pursuit system fails to differentiate them. But what is truly remarkable about this experiment and the one by Moore and Fallah is that stimulation did not just cause a move-

ment or a percept but caused the brain to commit its resources to one location.

Stimulating a cognitive step is an enormous leap for systems neuroscience. By analogy with previous microstimulation results, it places neurons in a causal loop and provides direct support for our interpretation of neural discharge based on correlative evidence. For example, the inference that ‘up’-preferring neurons in the visual cortex signal the evidence for an ‘upward’ perception was proven correct when it was shown that stimulating such neurons caused monkeys to choose ‘up’ in a discrimination experiment¹³. Previous recordings from neurons in the FEF led to the hypothesis that activity signals the selection of a location in the visual field for visual and motor function². Both the studies described here seem to indicate that this hypothesis is correct: an increase in spike rate from FEF neurons causes selection of an object at the location signaled by activity of the neurons, commitment to a sensory interpretation associated with that location, and possibly an orienting eye movement to that location.

Finally, let us note that this achievement is accomplished by targeting neurons in a motor area of the brain. A subversive band of neuroscientists have long suspected a deep connection between motor systems and cognitive processes that are traditionally regarded

in the domain of sensation and perception^{14,15}. In addition to the light they shed on the FEF, these microstimulation studies may boost enthusiasm for the idea that cortical ‘motor’ systems may be involved in directing ideas as well as body parts.

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Regenerating nerves follow the road more traveled

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An *in-vivo* imaging study shows that regenerating axons retrace their previous paths after nerve crush, apparently guided by the mechanical properties of endoneurial tubes.

Developing axons must navigate a complex embryo to locate and form synapses with appropriate targets. Over the last decade, there has been an explosion of molecular understanding of the guidance factors that create patterns of neuronal connectivity. Major classes of

factors include the ephrins, semaphorins, netrins, slits, RGMs, Ig-CAMs and integrin-binding extracellular matrix components^{1,2}. Such molecules can function in attractive or repulsive modes as diffusible, matrix-bound or cell-surface cues for growing axons. Gradients of such molecules, ‘read’ primarily by receptors on the axonal growth cone, create precise molecular addresses for innervation, and the refinement of synaptic patterns in terminal fields relies in part on activity-

dependent mechanisms. In contrast, mechanical or physical barriers have not been thought to be very important in development.

In this issue, Nguyen *et al.*³ provide evidence that physical factors are central in the regeneration of adult peripheral nerves. After axonal crush injury, functional recovery requires axons to succeed at the daunting task of re-navigating to the appropriate region and generating a new synapse at a precise postsynaptic target. In the peripheral nervous system (PNS), this does occur with some regularity, and a degree of functional recovery is typical. A prevailing notion is that axonal regeneration recapitulates development, as gene-expression studies confirm at least some similarities⁴. This implies that, after trauma, many of the same molecular guidance cues are at play during the re-establishment of axonal connectivity.

To explore the mechanism and fidelity of adult PNS axon regeneration,

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