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What electrical microstimulation has revealed about the neural basis of cognition

Marlene R Cohen and William T Newsome*

Neurophysiologists have shown repeatedly that neural activity in different brain structures can be correlated with specific perceptual and cognitive functions, but the causal efficacy of the observed activity has generally been a matter of conjecture. By contrast, electrical microstimulation, which allows the experimenter to manipulate the activity of small groups of neurons with spatial and temporal precision, can now be used to demonstrate causal links between neural activity and specific cognitive functions. Here, we review this growing literature, including applications to the study of attention, visual and somatosensory perception, 'read-out' mechanisms for interpreting sensory maps, and contextual effects on perception. We also discuss potential applications of microstimulation to studies of higher cognitive functions such as decision-making and subjective experience.

Addresses
Howard Hughes Medical Institute and Department of Neurobiology, Stanford University School of Medicine, Stanford, CA 94305, USA
*e-mail: bill@monkeybiz.stanford.edu

Abbreviations
FEF frontal eye field
MST medial superior temporal area
MT middle temporal visual area
QA quickly adapting
RF receptive field

Introduction

Since Penfield's pioneering electrical stimulation studies in human patients [1], it has been clear that artificially elicited neural activity can give rise to complex mental phenomena, including organized percepts, memories and experiences. During the ensuing decades, electrical stimulation proved to be very useful in the study of motor systems. Penfield's approach failed to generate substantial new insights into the neural basis of perception and cognition, however, because the gross electrical activation elicited by surface electrodes could not be related mechanistically to the information being processed within the excited neural tissue.

More recently, accumulating knowledge and advances in technology have provided novel opportunities to perturb cortical information processing in revealing ways through local extracellular electrical microstimulation. Since Penfield's time, for example, we have gained a wealth of detailed knowledge concerning the physiological properties of cortical neurons and how they are organized into intricate systems of columns and local circuits. Technical advances have allowed scientists to control the behavior of laboratory animals more effectively (e.g. eye/arm trackers, touch screens, etc.) and to deliver precisely controlled stimuli to the sensory surfaces. Exploiting these gains, investigators have conducted combined behavioral and physiological studies to correlate neural activity with specific perceptual and cognitive capacities, leading to precise hypotheses about the functional roles of various brain structures, circuits and cell types.

Many of these hypotheses can now be tested rigorously using electrical microstimulation, which allows investigators to perturb neural activity with considerable spatial and temporal precision while an animal performs a chosen behavioral task. Microstimulation is particularly powerful because it is the only tool presently available that allows investigators to measure the behavioral effects of an increase in the output signal of a group of physiologically characterized neurons. In this review, we summarize the progress that has been made using this approach, and we anticipate promising paths for future research.

Early studies of motion perception

The first use of microstimulation to link a specific aspect of perception (motion vision) to the activity of physiologically characterized neurons was for direction selective cells in the middle temporal visual area (MT), an extrastriate area of the primate visual cortex [2–5]. MT neurons respond optimally to motion in a particular 'preferred' direction within their receptive fields (RF). They are said to be direction-selective because they respond poorly or not at all to motion in the opposite, or 'null', direction. Furthermore, the MT is organized in a columnar fashion, so that neurons sharing similar preferred directions and receptive field locations are spatially clustered within the cortex, allowing a relatively homogeneous functional signal to be introduced by stimulating a cluster of neurons extracellularly.

In the initial microstimulation studies, monkeys viewed a dynamic random dot display in which some percentage of the dots moved coherently in one direction while the

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remaining dots moved randomly, providing a masking motion noise [2–5]. The stimulus was placed in the receptive field of the column of MT neurons being recorded, and the monkeys reported on each trial whether motion was in the preferred or null direction of the column under study. The key finding was that microstimulation of one or a few MT columns, delivered while the monkey viewed the random dot stimulus, could strongly bias the monkey's perceptual judgments toward the direction preferred by the stimulated column. Within limits, the probability that the monkey would report seeing one direction or its opposite could be varied monotonically by titrating the intensity of microstimulation (in amplitude or frequency of the current pulses) against the intensity of the coherent motion signal. These studies demonstrated conclusively that direction selective neurons contribute causally to the animal's reports of motion direction [2–5].

This finding was particularly significant because it provided definitive support for a central assumption that had undergirded sensory neurophysiology for the preceding 30 years: that the physiological properties of cortical neurons, studied one at a time, yield meaningful insight into the neural basis of perception. The significance of this step can be appreciated by considering the reaction of many engineers and physicists to the 'reverse-engineering' enterprise of single-unit neurophysiology: it seems akin to the notion that one can gain significant understanding of the function of a Cray supercomputer by removing the back panel and studying the individual components one at a time with a hand-held voltmeter. The notion appears somewhat whimsical at best and foolish at worst. Fortunately for neuroscience, evolution has created a brain with significant regularities (e.g. topographic maps, columns) that means that we can indeed detect and interpret meaningfully using the modest tools that are currently at our disposal.

Recent studies of discrimination performance

Most neuroscientists were quite surprised that microstimulation of one or a few cortical columns could influence discrimination performance so strikingly. Prevailing belief held that even a simple perceptual discrimination should involve a sufficiently complex network of neurons that the activity of any small group of neurons would be insignificant. Some suggested that the MT itself or motion perception in general might be 'special' in some way, following organizational or functional principles that differ from the norm for sensory processing in the cortex. This notion has been laid to rest by several recent studies. Celebrini and Newsome [6], for example, showed that direction judgments are influenced by microstimulation of direction columns in extrastriate area medial superior temporal (MST). Britten and van Wezel [7] provided evidence that microstimulation of MST neurons that

are tuned for optic flow parameters can bias a monkey's report of their direction of self-motion through the visual environment. Thus, microstimulation effects are not unique to MT. In addition, DeAngelis and co-workers [8] demonstrated that microstimulation of disparity-tuned columns in MT [9] can bias perceptual judgments of stereo-depth toward the depth plane encoded by the stimulated column, showing that microstimulation effects are not unique to motion vision.

In a particularly significant departure from regular practice, Romo and co-workers [10,11] extended the microstimulation approach to the analysis of functional circuitry within the somatosensory cortex. These investigators trained monkeys to discriminate the frequency of mechanical vibratory stimuli applied to skin of the hand. The monkeys were presented with two brief vibratory stimuli separated by a temporal delay and were rewarded for correctly reporting whether the first or the second stimulus had the higher frequency vibration. The ability to perform this discrimination in the 'flutter' frequency range (5–50 Hertz [Hz]) is thought to depend upon the discharge of quickly adapting (QA) neurons in primary somatosensory cortex (S1), which generate action potentials that are time-locked to the oscillations of the vibrating stimulus [12–14].
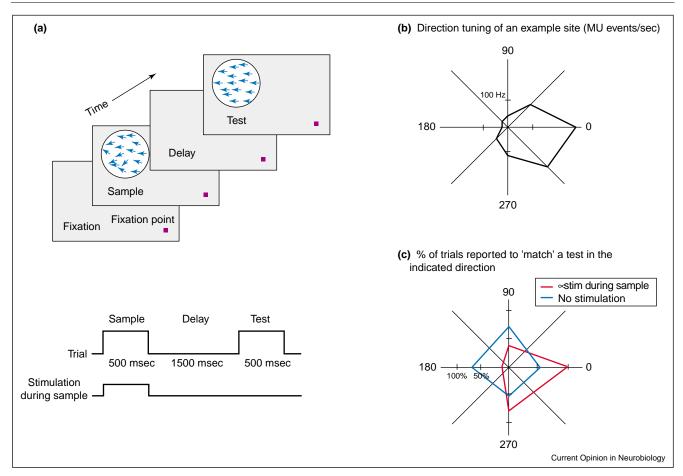
In an elegant set of experiments, Romo and co-workers [10,11] substituted microstimulation of cortical QA neurons for mechanical stimulation of the skin during one of the two temporal intervals, so that the monkey now attempted to discriminate the frequency of an artificial electrical stimulus delivered directly to the cortex from the frequency of a natural skin vibration. Remarkably, the monkeys did not miss a beat. They continued to perform the frequency discrimination as though the electrical stimulus were a mechanical stimulus applied directly to the skin. Furthermore, the monkeys continued to perform almost as well when microstimulation was substituted for both tactile stimuli, which indicates that microstimulation of QA neurons in S1 is sufficient to produce a perceptual experience that is both memorizable and discriminable. Importantly, stimulation of slowly adapting neurons in the cortex, which code vibration in a higher frequency range, caused the monkeys' performance to fall to chance levels within the flutter range, confirming Mountcastle's original proposal that QA neurons contribute specifically to the perception of flutter frequencies [12,13]. Thus far, this is the only system in which cortical microstimulation alone seems to produce sensations akin to those elicited by natural stimuli.

Delayed match-to-sample

Bisley, Zaksas and Pasternak [15••] revealed several important properties of MT microstimulation by employing a delayed match-to-sample paradigm that is commonly used in studies of visual working memory. In

Figure 1

Middle temporal visual area microstimulation biases motion perception. **(a)** Schematic of delayed match-to-sample task. After monkeys attained fixation, they viewed a random dot stimulus for 500 milliseconds (msec). The stimulus consisted of dots moving in a direction determined by a probability distribution whose mean was in one of the four cardinal directions. Following a 1500 msec delay period, the test stimulus was presented for 500 msec. The test stimulus consisted of dots moving coherently in either the same direction as the sample or the direction 180° opposite the sample. The monkeys indicated whether or not the test stimulus matched the direction of the sample by pressing a button. For each sample direction, half of the test stimuli were the same direction as the sample and half were in the opposite direction. On half of the trials, microstimulation was applied during the sample period (80 micro amperes [μA], 200 Hz). **(b)** Direction tuning of an example MT multiunit site. Firing rate (multiunit [MU] events/sec) is plotted against dot direction. The preferred direction of the cells at this site is for motion to the right or down and to the right. **(c)** Behavioral data from one experiment. The plot shows the percentage of trials on which the monkey reported that the test 'matched' the direction of the sample for each of the four possible sample directions. In the no stimulation condition (blue line), the monkey reported a match roughly 50% of the time for all four directions, leading to an average of about 90% correct as the test actually matched the sample exactly half the time. When microstimulation was applied (red line; same site whose tuning is depicted in [b]), the monkey reported a match for nearly every trial in which the test stimulus was rightward, and for most trials when the test stimulus was downward. By contrast, the monkey almost never reported a match when the test was leftward. This indicates that microstimulation during presentation of the sample biased the monkey's perception of the motion toward the preferred direction of the stimulated cells. (Data adapted from Bisley et al. [15••].)

this experiment, the monkey viewed a random dot stimulus moving in one of four possible directions (the sample), followed after a brief delay by a second 'test' stimulus (Figure 1a). The monkey pressed one of two buttons to indicate whether the direction of motion of the test stimulus was the same as or different from that of the sample. On non-stimulated trials, the monkey performed nearly perfectly because the motion stimulus was well above perceptual threshold and the angle between the sample and the non-matching test stimuli was large (at least 90 degrees). On some trials, microstimulation was applied to a direction column in MT during presentation of the initial sample stimulus, on other trials microstimulation was applied to the same column during the delay period. Stimulation applied during the 'sample' stimulus strongly influenced performance, causing the monkey to choose as a 'match' a test stimulus whose motion matched the preferred direction of the stimulated column rather than the direction of sample stimulus (Figures 1b and c).

This experiment is important for several reasons. First, the match-to-sample paradigm provides a more direct way to assess the perceptual experience of the monkey. The discrimination paradigm employed in earlier MT studies required the monkey to bin its perceptual judgments into somewhat abstract categories (e.g. left versus right), whereas the match-to-sample paradigm asks the monkey more directly ''what did the sample stimulus (+ microstimulation) look like?'' Second, this study demonstrated that microstimulation effects could be obtained even when the monkey performs a task that is well removed from psychophysical threshold. Finally, by using a button press as the operant response, the authors made the important point that MT microstimulation effects are independent of the particular motor act used as the operant response (all prior MT studies had used eye movements as the operant response).

Center-surround modulation and the influence of context

The microstimulation effects considered thus far have the common feature that the psychophysical task was tailored to the primary coding properties of the cells under study (i.e. direction cells — direction judgments; flutter vibration cells — flutter frequency judgments). Nearly all sensory neurons are thought to encode information other than their primary tuning property, and microstimulation can be used successfully to discern secondary coding properties of neurons.

Psychophysicists have long known that the perception of visual stimuli in a restricted region of space is strongly influenced by surrounding visual stimuli [16]. This perceptual observation is mirrored by the 'surround' properties of single cortical neurons. The response of a neuron to a particular stimulus within its receptive field can differ strikingly depending upon what stimuli are present simultaneously in adjacent regions of visual space, even though the surround stimuli alone elicit no overt response from the cell. This is true in MT where the responses of some columns to preferred direction motion are strongly suppressed if the moving stimulus extends into the receptive field surround [17,18]. These columns are termed 'local motion' columns because they seem to emphasize local motion contrast in the visual field. Other columns that lack surround suppression are thought to respond to 'global motion' of the entire visual field. A recent microstimulation study by Born, Groh and their co-workers [19] provides evidence that the surround properties of single cells might cause the psychophysical effects of visual context.

These investigators trained monkeys to initiate smooth pursuit eye movements to small targets moving in a variety of directions and speeds within the receptive field of a column of MT neurons. Importantly, the pursuit target moved over a background textured with stationary random dots. A very puzzling result emerged during the course of these experiments. Microstimulation of MT biased pursuit initiation toward the preferred-null axis of motion as anticipated; but oddly, biases toward the null direction (wrong-way effects) occurred nearly as often as biases toward the preferred direction (right-way effects). The investigators noticed that 'local motion' columns tended to generate the right-way effects and 'global motion' columns the wrong-way effects.

The investigators hypothesized that right-way effects occurred because stimulation of local motion columns caused motion to be attributed to the local feature in the visual field — the pursuit target. By contrast, stimulation of a global motion column caused motion to be attributed to the background dot pattern, 'inducing' a perception of oppositely directed motion of the pursuit target, just as moving clouds 'induce' oppositely directed motion of the moon. Behavioral experiments provided strong support for this interpretation. Brief motion of the textured background, which mimicked the time course and hypothesized effect of MT microstimulation, in fact induced wrong-way pursuit of a stationary target in the same monkeys. Thus, the data support the hypothesis that behavioral effects of visual context can be attributed in some cases to surround modulation (or lack thereof) at the single cell level.

'Read-out' mechanisms

Sensory areas of the cerebral cortex can be considered as representing evidence regarding the current state of the sensory world. Higher-level mechanisms (e.g. a 'decision' process) must interpret, or 'read out', this evidence to guide appropriate behavioral responses. Because microstimulation allows the experimenter to manipulate the sensory evidence in the map, it can be used to study the algorithms by which downstream areas interpret sensory activity.

Recent studies have sought to distinguish between two general algorithms for reading out activity in the motion map in MT: 'winner-take-all' (the strongest responding column wins the day) or 'vector averaging' (all columns contribute in proportion to the intensity of their responses). Groh *et al.* [20] examined pursuit and saccadic eye movements made to moving visual targets while the motion map was perturbed using microstimulation. Both the pursuit and the saccadic systems responded as though the motion of the target was intermediate between the real target motion and the motion vector inserted into MT through microstimulation. This finding provided evidence for a vector-averaging mechanism in the oculomotor context, which was confirmed in beautiful behavioral experiments by Lisberger and Ferrera [21]. By contrast, earlier microstimulation experiments by Salzman and Newsome [5] yielded strong evidence

for a winner-take-all mechanism in the context of a perceptual discrimination paradigm.

Nichols and Newsome [22•] provided a partial resolution of these conflicting results. These investigators employed a new version of the perceptual task that allowed a higher resolution read-out of the perceived direction of motion. In contrast to the earlier forced-choice tasks, the monkey was allowed to report any perceived direction of motion by making a saccade to a corresponding point along the perimeter of the visual stimulus aperture (the point toward which motion flowed). Nichols and Newsome obtained strong evidence for a winner-take-all mechanism when the motion vectors generated by visual and electrical stimulation differed substantially (> 135 degrees), but the data were consistent with vector averaging for smaller angular separations.

This series of experiments suggests that the sensory evidence within a single cortical map can be interpreted in different ways depending upon the exact nature of the conflicting motion signals in MT and the behavioral purpose for which the information is used (e.g. guidance of eye movements versus perceptual reports). An important caveat to all of these experiments, however, is that the exact spatial spread of microstimulation-evoked activity has not been measured directly. A distinction between winner-take-all and vector averaging mechanisms requires that visually and electrically evoked motion vectors are sufficiently localized to yield distinct 'bumps' of activity within the motion map in MT. Thus, current inferences about the read-out mechanism must be considered as provisional until such measurements can be made.

Attention

In a particularly innovative series of studies, Moore and co-workers [23,24••,25••] recently employed microstimulation to examine the neural systems that control visual attention. These investigators hypothesized that spatial attention can be manipulated through microstimulation of the frontal eye field (FEF), a primarily oculomotor structure from which saccadic eye movements are readily evoked by microstimulation. Moore and Fallah [23] first trained monkeys to attend to a peripheral target positioned amongst a field of blinking distracters and signal with a lever release when the target dimmed (Figure 2a). They then assessed effect of FEF stimulation on contrast threshold for detecting the dimming of the target when it was positioned either inside or outside the response field of the stimulation site. The microstimulation current was set to half of threshold for eliciting saccades so that accurate fixation was not disrupted by unwanted saccades.

Remarkably, Moore and Fallah [23,25••] found that FEF microstimulation improved the monkey's performance significantly when the target was positioned within the

FEF response field (Figure 2b), but had no effect or slightly impaired performance when the target was located outside the response field. It is difficult to attribute such stimulation effects to a direct modification of the sensory properties of the visual target (e.g. brightness or contrast) because accurate performance depends equally on knowing when the target does not change as well as when it does. The most parsimonious account of the data is that microstimulation of the FEF actually facilitates the allocation of attentional resources to the visuotopic location corresponding to the RF of the stimulated site.

Moore and Armstrong [24••] tested this notion by measuring the effects of microstimulation in the FEF on the visual responses of neurons in V4, an extrastriate visual area whose neurons are frequently selective for bars or edges of a particular orientation (Figure 2c). Because the activity of V4 neurons is modulated by spatial attention [26–28], the investigators hypothesized that FEF stimulation should influence the visual responses of V4 neurons in a similar manner. Consistent with this prediction, they found that FEF stimulation increased visual responsiveness, but only for those V4 neurons whose receptive fields spatially overlapped the RF of the FEF stimulation site (Figure 2d).
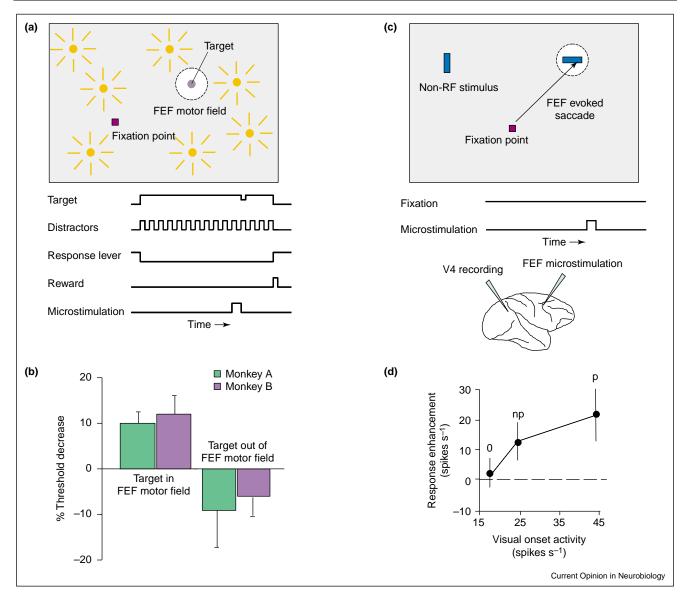
These are important findings for both scientific and technical reasons. The fact that stimulation of a structure that controls eye movements affects spatial attention suggests that the attentional and oculomotor systems might be inextricably linked [29,30]. If so, much of the current controversy over 'attentional' versus 'intentional' effects on neural activity in various brain structures could be misplaced. In most situations, both interpretations might be accurate. On the technical side, the study by Moore and Armstrong [24••] moves the field in a much needed direction. It is now common for investigators to identify neural activity in a given cortical area that modulates in tandem with a particular behavioral manipulation and could therefore play a role in mediating that behavior. It is uncommon, however, for investigators to test predictions of such models about the interaction between cortical areas. Coupling these two approaches has substantial potential for producing more incisive insights into the neural basis of mental functions.

Conclusions and future directions

Electrical microstimulation has emerged in the past decade as a powerful tool that allows experimenters to manipulate the activity of cells thought to mediate perceptual and cognitive abilities, establishing a causal link between the firing properties of those cells and a particular aspect of perception or cognition. Most readers will have noted that the successful examples considered in this review invariably exploit known structural regularities within the nervous system, such as cortical columns

Figure 2

Microstimulation of frontal eye fields affects covert spatial attention. **(a)** Schematic of the detection task. Monkeys fixated a spot of light and covertly attended to a target of varying contrast amid a field of blinking distractors. The monkey's task was to release a lever when the target dimmed. The target was placed either inside or contralateral to the response field of the FEF site being stimulated. On half of the trials a brief train of microstimulation pulses (50 msec train, 333 Hz) preceded the dimming of the target. Stimulation pulses were below the current threshold for eliciting saccades. **(b)** Changes by contrast detection thresholds for two monkeys following microstimulation when the target was placed either inside (left) or outside the stimulated FEF response field. When the target was inside the response field, stimulation decreased the threshold in both monkeys, indicating an increase in perceptual sensitivity. By contrast, when the target was outside the response field, stimulation slightly worsened detection thresholds slightly. These results suggest that stimulation directs the locus of the monkey's attention to the stimulated region of visual space. **(c)** Schematic of the protocol for determining the effect of FEF microstimulation on the visual responses of a V4 neuron. The receptive field of the V4 neuron (white circle) overlapped with the saccade vector (arrow) produced by stimulating a site in FEF. A bar of light in either the V4 neuron's preferred (horizontal bar in this example) or the non-preferred (vertical in this example) orientation was placed in the V4 neuron's receptive field, and a non-preferred stimulus was placed outside the receptive field. While the monkey fixated, the FEF site was stimulated with subthreshold current pulses (for eliciting saccades), and the effect on the visual responses of the V4 neuron was measured. **(d)** Average response enhancement of a V4 neuron following FEF microstimulation. The enhancement is plotted as a function of visual-onset activity when there was a preferred (p), non-preferred (np) or blank (0) stimulus in the V4 neuron's receptive field. (Data adapted from Moore and Fallah, Moore and Armstrong [23,24••].)

(direction, disparity, flutter vibration, center-surround modulation) or topographic maps (visual attention) to introduce a functionally meaningful signal into the cortical circuitry. This is probably an essential ingredient for

success with a spatially crude tool like extracellular microstimulation, which excites many neurons simultaneously (perhaps a few hundred at typical current levels) (see Discussion in [3]). Columns and maps are common

features of cortical organization, however, and it seems likely that additional important insights will continue to emerge from this type of study.

Recently, physiologists have begun a serious study of decision-making and the sensory and reward-related factors that impact it (Schultz, this volume; [31,32]). This area of inquiry will gather momentum in the future. First, decision making forms a crucial link between sensory and motor processing, which were previously distinct fields. Second, studying decisions provides an opportunity to link motivation and reward to measurable aspects of performance. Finally, this area of study benefits from a well-developed body of theory (decision theory and economic theory) that provides a basis for posing illuminating questions. Microstimulation techniques could be deployed in this emerging field in several ways. As a first-order question, one would like to know whether or not microstimulation of neurons that encode putative decision variables can actually change decisions in a predictable manner. While a result of this nature would be particularly revealing, it might be the case that decision-making activity is so widely distributed that the effects of microstimulation at a single location on biasing a decision will be minimal (preliminary results in our laboratory are mixed).

Microstimulation can, however, be used in more subtle ways to illuminate the neural mechanisms underlying decision making. In the context of a reaction time version of the direction discrimination task, for example, Shadlen and co-workers [33••] have shown that microstimulation in MT modifies reaction times in a way that is predicted from a specific 'integrator' model of how sensory signals are evaluated to generate decisions [34,35,36•]. A competing 'attractor' model [37] might make alternative predictions that could also be tested with microstimulation techniques.

In a somewhat similar vein, Tehovnik and Schiller and their co-workers [38–40] are using microstimulation to examine the influence of early cortical areas (V1 and V2) on decisions to saccade to competing visual targets. In their paradigm, two targets appear at varying times in the trial, and monkeys are rewarded for making a saccade to either target. Microstimulation under different conditions (varying cortical depths and current amplitudes) affects the monkeys' choices in different ways; some manipulations make it more likely that the monkey will choose the target in the stimulated receptive field, and some manipulations make it less likely that the monkey will choose the stimulated target. Important new information could arise from studies of this nature, although it is too early as yet to draw firm conclusions.

Although microstimulation is now established as a powerful tool for studying higher brain functions in laboratory animals, most experimenters who conduct such studies suspect that there is a great deal of important information to be had that we cannot extract from laboratory animals. Specifically, we wonder how manipulating cortical circuitry using artificial methods such as microstimulation affects the subjective experience of the monkeys as they perform their tasks. In the original MT microstimulation studies, for example, did the monkeys actually experience a vivid sensation of motion in a particular direction under the influence of microstimulation, or did they merely decide in favor of a particular direction regularly despite equivocal visual sensations?

In other words, we would like to have more insight into how conscious experience is altered by activity at selected points in the brain. Of the experiments considered in this review, the ones that come closest to obtaining this sort of information from monkeys are those of Romo and co-workers [10,11] (can the monkey compare electrical stimulation of the brain to direct stimulation of the skin?) and those of Bisley and co-workers [15••] (does the electrically modified motion stimulus look like this?). Nevertheless, substantial uncertainty remains about the subjective experiences caused by neural activity at specific locations in the brain. The development of a non-invasive technique to modify precisely and locally neural activity in humans will probably be necessary to address such questions satisfactorily.

Update
A new study by DeAngelis and Newsome [41] uses microstimulation to study mechanisms by which sensory information might be read out of a multi-dimensional sensory map. As discussed above, neurons in cortical area MT are selective both for the direction of visual motion and for binocular disparity. Using a direction discrimination task similar to those described in the main text, the authors found that microstimulation effects could be strongly modulated by the disparity tuning of the stimulated column even though disparity was completely irrelevant to the task. In two of the three monkeys, the best effects of microstimulation on directional judgments were obtained when the stimulated column was untuned for disparity. Thus, these two animals appeared to 'monitor' only a subset of direction columns while performing the task. (This observation could well account for some of the variability in the results of earlier MT microstimulation studies in which disparity tuning was not assessed.) In the third animal, microstimulation of direction columns was effective irrespective of disparity tuning, suggesting that this animal employed a less efficient strategy in which signals were pooled across all columns having an appropriate preferred direction. When microstimulation of a disparity tuned site did affect direction judgments (for all three monkeys), the effects tended to be stronger at the preferred disparity of the stimulation site than at a

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