

# Somatosensation: Touching the mind's fingers

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**Whether mental operations can be reduced to the biological properties of the brain has intrigued scientists and philosophers alike for millennia. New microstimulation experiments on awake, behaving monkeys establish causality between activity of specialized cortical neurons and a controlled behavior.**

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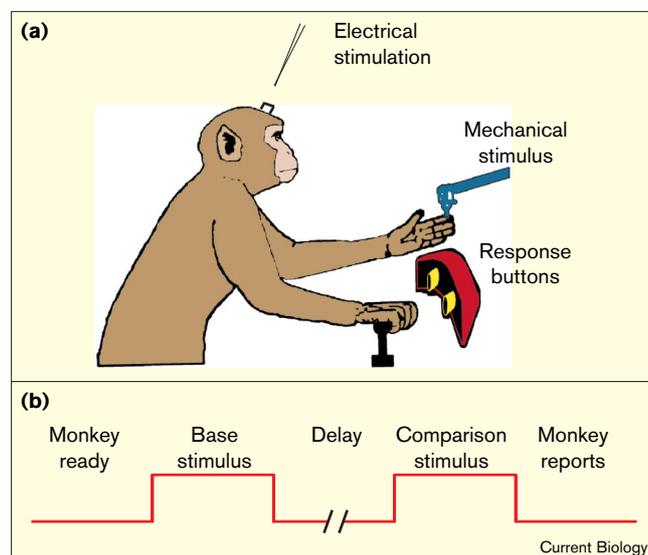
The most remarkable hypothesis of modern neuroscience is that the entirety of our personal experience — from our perception of the external world to our experience of internal thought — results solely from patterned electrical activity among the several billion neurons that comprise the central nervous system [1]. Ultimately, the most stringent test of this hypothesis is to create realistic experiences and mental operations artificially, by directly activating known circuits of neurons in the brain in the absence of the external inputs that normally elicit such mental operations. That artificial activation of brain tissue can elicit subjective sensations and organized memories was established by the pioneering studies of Wilder Penfield [2], who electrically stimulated various areas of the cerebral cortex in conscious human subjects during neurosurgical treatment of epilepsy. Penfield found, for example, that his patients reported vivid visual and auditory experiences when the cortex of the temporal lobe was stimulated. While Penfield's observations established a fundamental principle concerning the relationship of neural activity to mental experience, the relative crudeness of his electrical stimulation techniques, as well as the time limitations intrinsic to therapeutic surgery in humans, forestalled more serious attempts to map mental function onto precisely defined circuits of neurons.

Modern electrical stimulation techniques, combined with our increasingly rich knowledge of cortical anatomy and physiology, have now ushered in a powerful new generation of microstimulation experiments, including an intriguing new study by Ranulfo Romo and his colleagues at the National Autonomous University of Mexico [3]. These investigators employed a classic behavioral paradigm for studying the neural basis of somatosensory frequency discrimination that was first established by Vernon Mountcastle and his colleagues at Johns Hopkins University [4]. As illustrated in Figure 1, a behavioral trial begins when a

monkey indicates readiness by touching a post with its hand. A mechanical probe positioned on the smooth skin of a fingertip then vibrates at a specified 'base' frequency for 0.5 seconds, followed by a brief 'delay', or memory period of 1.5 to 3.5 seconds (Figure 1b). The probe then vibrates a second time at a specified 'comparison' frequency, after which the monkey touches one of two response buttons to report whether the comparison frequency was higher or lower than the base. Over the course of an experiment, twelve pairs of base and comparison frequencies are presented in pseudorandom order, with the lowest frequency being 6 Hz and the highest 44 Hz. The monkey receives liquid rewards following a correctly performed trial.

By design, the frequency range employed in these experiments (6–44 Hz) corresponds to the range that elicits the sensation of 'flutter vibration' in human subjects. Earlier experiments by Powell and Mountcastle [5] identified aggregates of neurons — cortical 'columns' — in monkey primary somatosensory cortex (S1) that responded optimally to stimuli vibrating in the flutter range. Quantitative

**Figure 1**



Experimental design. (a) Physical layout (adapted from [11]). (b) Sequence of events in a single trial. The monkey touches a handle to begin the trial. The base and comparison stimuli are delivered in sequence, separated by a brief delay period. The monkey then releases the handle and reports whether comparison frequency is higher than base frequency by pressing one of the two response buttons in front of him. The base and comparison stimuli can be delivered with a mechanical probe placed on a fingertip of the other hand (mechanical stimulus) or through an electrode placed in S1 (microstimulation).

analysis of neural responses suggested that this specific set of cortical neurons — ‘quickly adapting’, or QA neurons — is responsible for the psychophysical sensation of flutter vibration. In contrast, other columns, populated by ‘slowly adapting’ neurons, were thought to mediate the sensation of steady pressure on the skin.

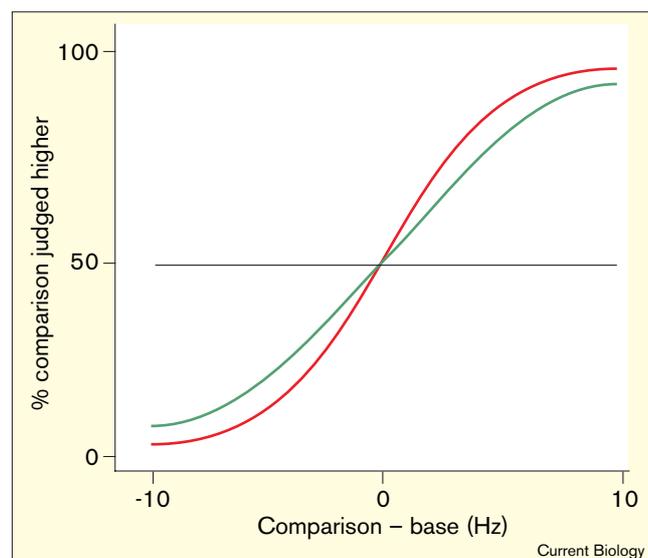
Romo and colleagues [3] have now employed electrical microstimulation techniques to test rigorously the hypothesized relationship between the activity of cortical QA neurons and the sensation of flutter. In their initial set of experiments ([6], see also [7]), the investigators positioned a stimulating electrode within a column of QA neurons in primary somatosensory cortex (S1), and substituted electrical stimulation of that column for the ‘comparison’ mechanical stimulus in the standard behavioral paradigm (Figure 1), on which the monkeys were already well trained. On each trial, the electrical stimulating pulses were delivered in a regular temporal pattern that mimicked one of the flutter frequencies delivered to the skin surface in the standard paradigm.

Remarkably, Romo and colleagues [6] found that the monkeys continued to perform the discrimination task nearly perfectly over a broad range of frequencies, even though the ‘comparison’ frequency was an artificial signal delivered directly to QA neurons in the cerebral cortex. The monkeys adapted to this new situation quickly, with no indication of a ‘re-learning’ period. These observations suggest strongly that the subjective sensations evoked by electrical stimulation of QA neurons are similar to those elicited by natural stimulation of the skin in the flutter range. Thus the results provide support for Mountcastle’s original hypothesis that the activity of QA neurons underlies the sensation of flutter vibration.

In a new set of experiments, Romo and colleagues [3] substituted cortical microstimulation for *both* the base and comparison mechanical stimuli in the standard paradigm. This procedure ups the ante considerably. The previous experiment showed that an electrical stimulus delivered to the cortex could be compared to a natural stimulus that was sensed and represented in working memory through normal processing mechanisms. For the monkey to perform accurately under the conditions, however, the brain must first characterize quantitatively the frequency of the base electrical stimulus, represent the frequency accurately in working memory, and make a successful comparison with the frequency of the second electrical stimulus. In other words, the full range of cognitive processes — perception, working memory and comparative decision-making — must be initiated and consummated on the basis of artificial stimuli delivered to specific columns of the somatosensory cortex.

Again, Romo and colleagues [3] found that the monkeys switched to the new condition with ease. Furthermore,

Figure 2



A schematic representation of the results obtained by Romo *et al.* [3]. The percentage of trials in which the monkey reports that the comparison frequency is higher than the base frequency is plotted as a function of the difference between comparison and base frequencies. A steep psychometric function, like the red curve in the figure, indicates excellent performance. This performance is typically obtained when both the base and comparison stimuli are delivered to the skin with a mechanical probe. When both stimuli are delivered via microstimulation of QA neurons in primary somatosensory cortex, performance is only slightly worse (green curve), still well above chance. Chance performance (black curve) is obtained when the stimulus is delivered via electrical stimulation of slowly adapting neurons in somatosensory cortex.

their frequency discrimination performance was nearly as good with the electrical as with the mechanical stimuli (Figure 2). In an important control experiment, the investigators replaced the mechanical ‘base’ stimulus with microstimulation to columns of *slowly adapting* neurons (also located in S1), while still delivering the ‘comparison’ stimulus with the mechanical probe. In such trials, frequency discrimination performance was essentially at the chance level (Figure 2). Electrical stimulation, therefore, can serve as a basis for flutter frequency discrimination only when applied to QA neurons; stimulation of randomly selected sites in somatosensory cortex is not sufficient.

These microstimulation studies are exceedingly pleasing to the sensory neurophysiologist. After decades of painstaking research, it is gratifying to realize that we understand a sensory system in sufficient detail to generate quantitatively precise behavior employing only artificial activation of specific sites in the cerebral cortex. Beyond the elegance of the behavioral techniques and the pleasure of the experimental results, however, a skeptic might reasonably ask whether these experiments have revealed to us any fundamentally new principle of cortical function. Certainly Penfield’s early work has already established the

general connection between perceptual experience and electrical activity in the cerebral cortex. Similarly, electrical stimulation of single nerve fibers in the human skin has already shown that peripheral QA fibers carry the signals that lead ultimately to the sensation of flutter vibration [8,9]. What, exactly, is new in the recent experiments from the Romo laboratory?

The new studies are valuable for several reasons. First, the behavioral results of microstimulation can be related to cortical neurons with specialized physiological properties (QA). In contrast, Penfield's stimulation techniques were sufficiently gross, and his knowledge of cortical physiology sufficiently limited, that he could only speculate in general terms about the nature of the neural processing that led to the stimulation-evoked experiences reported by his subjects. Second, the new studies establish a compelling 'psycho-neural' relationship at a substantially more central location in the nervous system than did the earlier studies of peripheral QA fibers in humans. Given the substantial convergence and divergence in anatomical connections between the somatosensory periphery and S1, this result was by no means assured. To the extent that these relationships can be demonstrated progressively more centrally, we become more certain of our progress in understanding the complex circuitry of the cerebral cortex. Third, the electrically-evoked sensations supported impressively precise frequency discrimination (Figure 2). Plainly, frequency discrimination of electrical stimuli is not simply a crude imitation of the 'real thing'.

Finally, Romo and colleagues' studies raise the possibility that similar techniques can be used to analyze circuitry underlying the higher cognitive processes of working memory and decision-making. For example, electrophysiological recordings in the prefrontal cortex have revealed neurons that appear to encode the frequency of the base stimulus during the delay period of the discrimination task (Figure 1): the firing rates of these neurons vary monotonically as a function of the base frequency [10]. Might it be possible to influence or change the monkey's memory by electrically stimulating such neurons? This is an experiment worth trying, but it may prove difficult for at least two reasons. First, the circuits involved in working memory may be distributed over a wider range of cortical areas and columns than the S1 circuits that comprise the initial sensory representation. Secondly, we do not yet know whether the prefrontal neurons that are active during the delay period are indeed aggregated into cortical columns, or whether they are scattered amongst other neurons of unrelated function. Diffuse organization of either variety would reduce the chances of obtaining convincing microstimulation effects (with single electrodes, at least).

Nevertheless, the power of the microstimulation technique to establish causality between neural activity and behavioral

performance encourages a determined effort at such experiments. Only a few years ago, the complexity of the cerebral cortex would have led most sensory physiologists to declare Romo and colleagues' current microstimulation experiments a fantasy. For now, all bets are off until the experiments are actually tried.

## References

1. Crick F: *The Astonishing Hypothesis*. New York: Scribners; 1994.
2. Penfield W, Perot P: **The brain's record of auditory and visual experience**. *Brain* 1963, **86**:595-696.
3. Romo R, Hernandez A, Zainos A, Brody CD, Lemus L: **Sensing without touching: psychophysical performance based on cortical microstimulation**. *Neuron* 2000, **26**:273-278.
4. Mountcastle VB, Talbot WH, Sakata H, Hyvarinen J: **Cortical neuronal mechanisms in flutter-vibration studied in unanesthetized monkeys. Neuronal periodicity and frequency discrimination**. *J Neurophysiol*. 1969, **32**:452-484.
5. Powel TPS, Mountcastle, VB: **Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: a correlation of findings obtained in a single unit analysis with cytoarchitecture**. *Bull Johns Hopkins Hosp* 1959, **105**:133-162.
6. Romo R, Hernandez A, Zainos A, Salinas E: **Somatosensory discrimination based on cortical microstimulation**. *Nature* 1998, **392**:387-390.
7. Wickersham I, Groh JM: **Neurophysiology: Electrically evoking sensory experience**. *Curr Biol* 1999, **8**:R412-414.
8. Ochoa J, Torebjork E: **Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand**. *J Physiol* 1983, **342**:633-654.
9. Vallbo AB, Olsson KA, Westberg KG, Clark FJ: **Microstimulation of single tactile afferents from the human hand**. *Brain* 1984, **107**:727-749.
10. Romo R, Brody CD, Hernandez A, Lemus L: **Neuronal correlates of parametric working memory in the prefrontal cortex**. *Nature* 1999, **399**:470-473.
11. Merchant H, Zainos A, Hernandez A, Salinas E, Romo R: **Functional properties of primate putamen neurons during the categorization of tactile stimuli**. *J Neurophysiol* 1997, **77**:1132-1154.