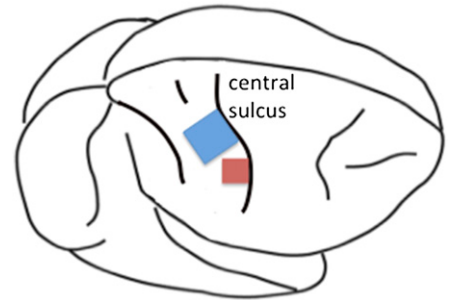


# Making sense: Determining the parameter space of electrical brain stimulation

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**Fig. 1.** Placement of microelectrode arrays by Kim et al. (9) over macaque primary somatosensory cortex.

Conscious sensory experiences are the bountiful subject of countless works of art, music, poetry, and other creative endeavors. The subject of how these experiences emerge is no less compelling. Perceptual qualia arise from the electrical activity of one (1) or, likelier, many (2) neurons in the brain. This observation has been most widely studied in visual cortex (3), where a number of papers have described the causal relationship between neural activity and perceptual behaviors, namely, detection and discrimination of electrically activating, spatially discrete neural populations. Topographic organization, as seen not only in the retinotopy of visual cortex but in the tonotopy of auditory cortex and the somatotopy of somatosensory cortex, renders all (especially primary) sensory areas potent model systems for determining the quantitative relationship between neural activity and perception. In select human subjects, where it is possible to ascertain directly the relationship between neuronal selectivity and sensory qualia, topography (or perhaps attendant columnar microstructure) appears to be critical. Rudimentary (single electrode and brief, unpatterned pulse train) stimulation of a spatially contiguous population of neurons generates percepts in areas with exquisite retinotopy, for example, but not in areas where visual representations become more spatially diffuse (4). Electrical stimulation of clustered representations of sensory space may be more readily interpretable by the experimental subject, because it more closely mimics the natural sensory activation of neurons (but refer to 5). Similarly, in primary somatosensory cortex, it is thought that detection and discrimination of electrical pulse trains is facilitated by its modular organization and is indistinguishable from mechanical sensory stimuli (6, 7). In areas downstream of primary sensory cortices, activity may naturally be more spatially and temporally distributed and very unlike the simple patterns of electrical stimulation that are experimentally delivered. This finding bears important implications for placement

of minimally invasive brain/machine interfaces (BMIs) or cortical prostheses, particularly when damage to the peripheral nervous system or spinal cord distorts, impairs, or completely obviates natural sensory experiences but spares sensory cortex. In some clinical situations, however, it is undesirable to produce readily detectable (illusory) stimulation of cortical neurons. For instance, in closed-loop “responsive neurostimulation” in cortex and deeper structures in medically refractory epilepsy, electrical stimulation is used to abort intractable seizures (8), and is ideally imperceptible to the patient. It is absolutely essential to establish the most safe and effective electrical stimulation protocols in nonhuman primates that can be applied to both cortical devices that can reproduce sensory experiences and devices that can activate neurons indiscernibly. In PNAS, Kim et al. (9) explore the parameter space for safe intracortical microstimulation of primate somatosensory cortex in a detection and discrimination paradigm.

Electrical stimulation in nonhuman primate visual cortex has provided tremendous insight into the causal relationship between neural activity and sensory perception. Visually guided behaviors are of exquisite ethological relevance for primates, and, accordingly, of all sensory modalities, visual information occupies the greatest extent of cortical real estate. For both of these reasons, most work relating neural activity to sensory behavior has been performed in primate visual cortex. More recently, these studies have married electrical stimulation to careful quantitative approaches to behavior, using forced choice tasks that enable thresholds for detection to be ascertained without the influence of an unpredictably shifting reporting criterion (5, 10). Parameters for detection of electrical stimulation in primary visual cortex have been studied extensively (11), but, to date, there has been no comparable effort to detail the detectability and discriminability of electrical stimulation of primary somatosensory cortex. Notably, a series of papers demonstrated now

over a decade ago (6, 7) that somatosensory cortical microstimulation is discriminable at current amplitudes at least one order of magnitude greater than thresholds for detection observed in visual cortex.

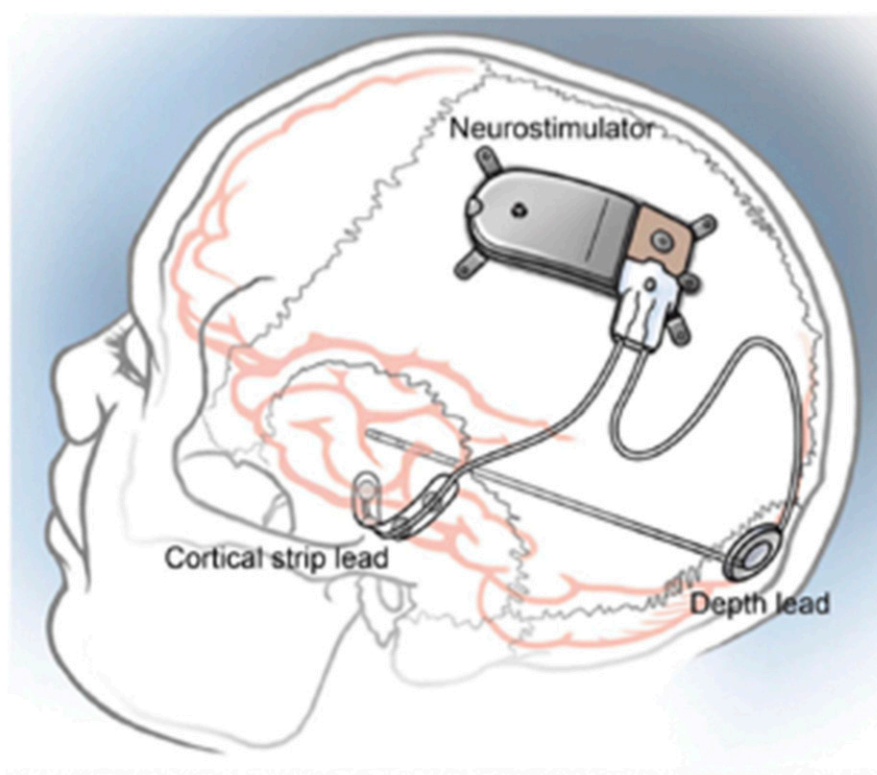
Kim et al. (9) used intracortical microstimulation to determine thresholds for detection of electrically activated neurons while nonhuman primates performed a two-alternative, forced-choice detection or discrimination task. Constant current pulses were delivered through electrode arrays placed over the functionally identified hand area of the somatosensory homunculus in areas 1 and 3b (Fig. 1), between which this group has demonstrated previously that detection thresholds with varying current amplitudes are similar (12). Pulse width and frequency and pulse train duration were varied parametrically here, revealing that thresholds for detection decrease as the magnitudes of these parameters increase. The most efficient charge transfer was achieved with shorter pulses and lower frequencies, however, with detection thresholds plateauing around 20–40  $\mu\text{A}$ , with pulse width around 200  $\mu\text{s}$ , frequency around 250 Hz, and duration around 200 ms. Faradic charge transfer is important to consider, because it correlates with damage at the electrode/tissue interface. Anodal phase leading pulses produce higher thresholds for detection than cathodal phase leading pulses, which is another feature that can be exploited to titer the detectability of microstimulation.

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See companion article on page 15202.

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**Fig. 2.** Placement of cortical subdural strip electrodes with responsive neurostimulation in medically refractory epilepsy. Image courtesy of NeuroPace, Inc.

Apart from simple detection of electrically activated neurons in somatosensory cortex, determining the parameter space for discrimination of microstimulation offers to provide basic details on how to reproduce readily detectable but qualitatively distinct natural sensory experiences more faithfully. Amplitude, frequency, and pulse train duration of detectable stimuli in a microstimulation discrimination task produced just noticeable differences (JNDs) that were indistinguishable between two functionally distinct areas of primary somatosensory cortex (areas 3b and 1). This finding suggests that (like for detection) direct stimulation of either area could be used to produce discriminable percepts. Interestingly, JNDs remain relatively independent of stimulus amplitude and frequency, whereas discrimination performance improves as a function of stimulus duration, plateauing at  $\sim 300$  ms, consistent with the idea that sensory discrimination requires longer integration times than detection.

The readily titratable thresholds for detection and discrimination and the ability to electrically activate two distinct primary somatosensory regions with comparable behavioral effects highlight the flexibility of direct cortical activation. Although there is not yet a clinically useful somatosensory BMI in which electrical stimulation aims to replace, augment, or alter natural stimulation, there is currently

an application in which it is unfavorable to produce a detectable percept. Therapeutic closed-loop responsive neurostimulation involves implantation of a device that records and aborts seizure activity in epileptic cortex in patients who are refractory to antiepileptic drug therapy (Fig. 2). In this circumstance, it is important to know how electrical stimulation parameters that effectively abort seizures can be titrated to avoid producing illusory percepts. The fact that either area 3b or area

1 can be stimulated with similar behavioral consequences is also useful. Given their locations (13) in the fundus of the central sulcus and crown of the rostral bank of the postcentral gyrus, respectively, it may be surgically easier to access the latter for a somatosensory BMI.

The authors concede that the artificially applied patterns of electrical activity produced in their detection and discrimination tasks are likely dissimilar from natural mechanical sensory stimuli (9). However, work in the visual system suggests that the plasticity of cortex enables a motivated subject to learn how to detect and discriminate electrically evoked sensory percepts that are distinct from natural stimulation (4, 5, 14–16). The implications for a cortical prosthetic are notable. Even if the qualia produced by electrical stimulation do not faithfully recapitulate sensory stimulation from the periphery, patients can learn to detect and discriminate (in association with valence and reward) different kinds of electrical stimulation in somatosensory cortex.

The electrophysiological effect of cortical microstimulation has been shown to be restricted to a volume tens of micrometers in diameter (17), consistent with the size of a visual cortical column. However, the cell type-specific populations of neurons activated with this kind of stimulation remain unknown. As the activity of neurons can be ever more precisely controlled with genetically targeted optical strategies (18), biological and technical challenges remain that make these approaches still unsafe for applications in human disease. Kim et al. (9) provide an important first effort to determine the parameters for safe and behaviorally relevant electrical activation of neurons in primary somatosensory cortex.

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