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Insights into cortical mechanisms of behavior from microstimulation experiments

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Abstract

Even the simplest behaviors depend on a large number of neurons that are distributed across many brain regions. Because electrical microstimulation can change the activity of localized subsets of neurons, it has provided valuable evidence that specific neurons contribute to particular behaviors. Here we review what has been learned about cortical function from behavioral studies using microstimulation in animals and humans. Experiments that examine how microstimulation affects the perception of stimuli have shown that the effects of microstimulation are usually highly specific and can be related to the stimuli preferred by neurons at the stimulated site. Experiments that ask subjects to detect cortical microstimulation in the absence of other stimuli have provided further insights. Although subjects typically can detect microstimulation of primary sensory or motor cortex, they are generally unable to detect stimulation of most of cortex without extensive practice. With practice, however, stimulation of any part of cortex can become detected. These training effects suggest that some patterns of cortical activity cannot be readily accessed to guide behavior, but that the adult brain retains enough plasticity to learn to process novel patterns of neuronal activity arising anywhere in cortex.

Keywords

Microstimulation; Cerebral cortex; Macaque; Monkey; Human; Detection; Perceptual learning; Plasticity; Perception; Electrical stimulation; Neuronal coding; Sensory coding

1. Introduction

Electrical microstimulation has long been an important tool for exploring the organization and function of the nervous system. The ability to perturb activity within a system can provide important insights into the contributions of its components. In studies of the brain's circuitry, microstimulation has provided greater spatial and temporal precision than other techniques that alter activity, such as lesions or pharmacological agents.

Microstimulation has been a mainstay in studies of the organization of motor systems. It has also been used in trained, behaving subjects to explore how specific populations of neurons contribute to sensory and cognitive processing. In addition to assigning perceptual or motor contributions to specific neurons by altering activity at specific brain sites, it has also been used to study how readily activity inserted into different brain structures can be behaviorally detected and discriminated. These studies provide information about how brain structures integrate and process neuronal activity.

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Here we will focus on insights that have come from electrical microstimulation of cerebral cortex in behaving subjects. Although we focus on cerebral cortex, most of the approaches and the results are likely applicable to other brain structures. We discuss studies that provide information about the differences and commonalities between different cortical regions. Microstimulation studies support the idea that each region of cerebral cortex represents a distinct type of sensory, motor or cognitive information that can be used to guide behaviors. We will also consider microstimulation experiments that investigate the plasticity of adult cerebral cortex and the extent to which it can accommodate different spatiotemporal patterns of neuronal activity.

By limiting ourselves to specific types of microstimulation experiments in cerebral cortex, our discussion will be far from an exhaustive treatment of stimulation experiments. We focus on experiments that use electrical microstimulation rather than transcranial magnetic stimulation or optogenetic methods (see Fenno et al., 2011; Yizhar et al., 2011; Pell et al., 2011). Additionally, we primarily consider experiments that explore the relationship between cortical activity and behavior, rather than those that use microstimulation to establish functional connectivity between brain regions (see Clark et al., 2011). The general topic of electrical microstimulation has been considered in other recent reviews of technical considerations (Merrill et al., 2005; Tehovnik et al., 2006) and scientific results (Cohen and Newsome, 2004; Tehovnik and Slocum, 2006; Clark et al., 2011).

2. The effects of microstimulation on neurons

To interpret results from microstimulation experiments, we must understand the spatial and temporal distributions of the neuronal activity microstimulation creates. We therefore begin with a discussion of how microstimulation alters neuronal activity.

The number of neurons activated by microstimulation and their distribution in cortex depend on many stimulus parameters. Electrical stimulation parameters often differ between experiments, complicating comparisons between studies. To minimize such complications, most of the experiments discussed below involve similar stimulus parameters. Almost all use trains of constant current pulses delivered through extracellular microelectrodes at rates from tens to hundreds of Hertz for periods from tens to hundreds of milliseconds. The pulses are typically brief (100–200 μs) and biphasic to avoid irreversible reactions at the metal surface (Merrill et al., 2005), with the cathodal current first. The currents delivered are generally between 1 and 100 μA. Deviations from these ranges will be highlighted when relevant.

2.1. Direct and indirect activation

When considering how microstimulation affects behavior, it is useful to distinguish between the direct and indirect effects of microstimulation on neurons. The direct effect on neurons is caused by current flowing from the microelectrode tip and changing the membrane potential of neurons. The change in membrane potential depends strongly on the distance between the electrode and a neuronal element, as well as the time derivative of stimulation intensity (Rattay, 1999). This direct effect of stimulation can be thought of as an intracellular current injection associated with each stimulus pulse, which can depolarize cells enough to make them spike.

Microstimulation can directly affect synaptic release by direct depolarization of synaptic terminals, by passive intracellular spread of current to nearby presynaptic sites, or by action potentials produced near the microelectrode that propagate to more distant synaptic sites. Regardless of how the stimulus is communicated to the synapse, the resulting synaptic

activity in directly excited neurons can indirectly affect the activity of many postsynaptic neurons and cause them to spike.

The indirect neuronal spiking resulting from electrical microstimulation can vastly exceed the direct neuronal activation. In principle, a single action potential produced directly by microstimulation might be repeatedly amplified in subsequent structures to produce millions of spikes (London et al., 2010). For example, when a subject gives a spoken or written report of a percept produced by microstimulation, all the neuronal activity associated with producing that report can be considered to be indirectly driven by the microstimulation. However, little would be gained by trying to map all the indirect activity back to the site of microstimulation.

Because the behavioral consequences of microstimulation almost always depend on indirect activation that extends relatively broadly in space and time compared with the activity of neurons driven directly by the microstimulation, the interpretation of microstimulation might seem intractable. However, regardless of the extent of indirect activity, any specific percept, movement or other change in behavioral state that occurs reliably when a brain site is stimulated can be said to be caused by the neurons that are directly activated by that stimulus. This ability to infer that specific neuronal activity caused a specific effect is the most important and distinguishing attribute of microstimulation as a technique for studying brain function.

Intense or chronic electrical stimulation can cause indirect activity in the form of seizures or other pathological activity. The weak electrical stimulation considered here activates surrounding cortical tissue while it is delivered, but does not cause a measurable afterdischarge in the EEG or induced epileptiform activity (“kindling”, Bartlett et al., 2005; Mares and Tolmacheva, 2007), which are seen with much more aggressive stimulation. In experiments designed to produce kindling in monkeys, stimulating with long (1–60 s) trains of strong current (>5 mA) failed to produce seizures, and only after stimulating daily with more than 500 μA for 6 months were clonic convulsions regularly produced (Goddard et al., 1969; see McNamara et al., 1980). A strong argument against kindling being a factor in the type of microstimulation experiments considered here comes from work in which monkeys are trained to do a two-interval forced choice task in which they report which of two closely spaced 250 ms intervals contained an electrical stimulus (Murphey and Maunsell, 2007; Murphey and Maunsell, 2008, described in detail below). The fact that animals can detect randomly-selected stimulus intervals in a region of cortex where stimuli have been applied thousands of times effectively rules out pathological activity such as kindling.

2.2. The volume of directly activated neurons

In later sections we will discuss how microstimulation has been used to show that groups of neurons separated by small distances in cortex can cause widely different percepts or movements. Interpreting these effects requires an understanding of the number and spatial distribution of neurons directly activated by the stimulus. Physiological studies have shown that most of the directly activated neurons in cortex are in the immediate vicinity of the stimulating electrode.

Using one electrode for stimulating and another for recording, Stoney and colleagues (1968) reported that a single 200 μs cathodal pulse of 10 μA directly activated most of the neurons that were within 80–90 μm of the stimulating electrode’s tip. Larger currents increased the activated radius. These results served as the basis for estimates that currents from 2 to 150 μA would activate neurons within 50–500 μm of a stimulating electrode, corresponding to 60–62,000 neurons in monkey V1 (Tehovnik and Slocum, 2007). However, results from

two-photon calcium imaging experiments suggest that microstimulation causes spiking in fewer neurons than suggested by these electrode recordings.

Two-photon calcium imaging makes it possible to see all of the neurons that are active within a single plane near an electrode. Such imaging of cortex during weak microstimulation (tens of microamps) shows that only a small fraction of the neurons in the vicinity of a stimulating electrode are activated (Histed et al., 2009), on the order of tens to hundreds of sparsely distributed neurons that are predominantly within a few hundred microns of the stimulating electrode. Because the subset of active neurons changes when the electrode is advanced tens of microns, it seems likely that most of the directly activated elements are axons that pass close to the electrode tip (fibers of passage). Modeling and in vitro work support the idea that axons are more sensitive to standard biphasic stimulus pulses than are cell bodies (Nowak and Bullier, 1998; Rattay, 1999; McIntyre and Grill, 2000). It is not clear why the earlier study concluded that most neurons near the electrode tip were activated. However, those investigators did note that they could not drive most of the neurons they encountered, although they attributed this to the recording and stimulating electrodes diverging in uncontrolled ways (Stoney et al., 1968).

Two-photon imaging also makes it possible to measure how many neurons in the vicinity of a stimulating electrode are driven directly versus indirectly. Blocking synaptic transmission has little effect on the number of neurons activated by microstimulation (Histed et al., 2009), showing that most of the spiking neurons in the vicinity of a stimulating microelectrode are driven directly by stimulating currents near threshold. The absence of synaptically-driven spiking at low currents is consistent with observations of relatively sparse and weak connections between proximate cortical neurons (Ts'o et al., 1986; Galarreta and Hestrin, 1998).

While most of the cells directly activated by microstimulation lie close to the stimulating electrode, two-photon calcium imaging shows that stimulation with low currents can also reliably drive cell bodies that are millimeters away (Histed et al., 2009), presumably by stimulating their axons. Behavioral studies discussed below suggest that the effects of microstimulation are dominated by more localized neurons, with many effects arising from only a few cortical columns (e.g., ~250 μm). Such selective behavioral effects likely reflect the concentration of activated neurons immediately around the stimulating electrode tip. Because postsynaptic effects typically require the summation of many inputs, the downstream effects of stimulation might depend on the relatively closely spaced activated neurons immediately around the electrode tip. The widely spaced activated cells far from the electrode might be sufficiently sparse that they do not converge on the postsynaptic neurons. This is one way that the effects of microstimulation may be influenced by the mapping of neurons' response properties within a cortical area, as well as the topography of projections from one area to another.

2.3. Indirect effects: Spatial extent and inhibition

Voltage-sensitive dye (VSD) imaging has provided data on subthreshold effects of microstimulation, revealing widespread activity across the brain as a result of stimulation (Seidemann et al., 2002; Ferezou et al., 2007). Because VSD signals are thought to primarily reflect synaptic input to cells (see Chemla and Chavane, 2010), this activity is likely dominated by subthreshold (non-spiking) effects. In contrast, two-photon calcium imaging primarily measures suprathreshold spiking (Helmchen et al., 1999), and experiments using this method find a sparser set of spiking neurons that is primarily activated via direct depolarization (Gobel and Helmchen, 2007; Histed et al., 2009). When synaptic transmission is blocked pharmacologically, VSD effects are drastically reduced (Ferezou et al., 2007) but calcium responses are largely unchanged (Histed et al., 2009). This suggests

that much of the subthreshold activity arises via synaptic transmission and is therefore indirect. Similarly, fMRI studies monitoring blood oxygenation level dependent (BOLD) signals see responses to relatively robust stimulation of V1 (1 mA, 4 s stimulus trains) up to 1–3 mm from the stimulation site (Tolias et al., 2005). In experiments with visual stimuli the majority of the BOLD response, particularly its later phases, appears to correlate well with subthreshold activity (Logothetis, 2002). Stimulation with high currents likely recruits a large amount of such postsynaptic activity.

Combining microstimulation with fMRI provides a powerful way to reveal the connections between different brain structures. Strong V1 microstimulation produces BOLD activity in topographically corresponding sites in extrastriate cortex that are directly connected with V1 (Tolias et al., 2005). Microstimulation with fMRI has also been used to reveal the connectivity between cortical sites that have similar response properties. Functional imaging studies have shown that visual cortex in non-human primates contains several small regions of face-selective neurons (Tsao et al., 2006). When one of these regions is microstimulated, fMRI measurements show activation localized within other face patches and not in intervening regions (Moeller et al., 2008), suggesting a high degree of specificity in the connections of these regions.

Another type of postsynaptic response to electrical stimulation is the long-latency inhibition that follows stimulation with relatively high currents (Berman et al., 1991; Volgushev etal., 1993; Chung and Ferster, 1998). The relative magnitude of post-stimulus inhibition depends on how many neurons are activated by the stimulation and the number of spikes produced by repetitive trains (Phillips, 1959). Using fMRI and electrophysiological recording, Logothetis and colleagues (2010) showed that electrical stimulation can produce either excitation or inhibition in distant downstream sites depending on the number and frequency of stimulus pulses and whether the target receives direct or indirect innervation from the stimulated structure. The magnitude of inhibition relative to excitation typically becomes larger with more intense stimulation.

3. Microstimulation mimics effects that drive neurons naturally

3.1. Microstimulation of primary cortical areas

The first important use of electrical stimulation of the surface of cerebral cortex was in the 19th century, when it was used to identify motor cortex and map the topographic representation of the body within it (see Berlucchi, 2010; Graziano, 2006). The classic studies of Penfield and colleagues in the middle of the 20th century greatly extended this work by stimulating the surface of cortical sensory areas in patients who were awake and could report their experiences. These studies demonstrated that stimulation of primary somatosensory, auditory or visual cortex could produce simple percepts such as vibrations, tones, or a small spot of light.

The key observation from these experiments was that the stimulation-induced percepts were similar to the percepts elicited by the physical stimuli most effective at driving the corresponding brain region. Percepts were appropriate for the sensory modality that drove responses in neurons in the stimulated cortical area. In addition, the evoked percept matched the receptive field location of neurons in the microstimulated site, following the topographic organization within a sensory area. It was the work of Penfield and his colleagues that produced the familiar mapping of homunculi across motor and somatosensory cortices.

Topographic organization is also obvious in microstimulation of V1. Stimulation of the surface of V1 produces the sensation of a small point of light, or phosphene, and the apparent position of the phosphene in the visual field corresponds to the established

mapping of the visual field onto V1 (Penfield and Perot, 1963; Brindley and Lewin, 1968; Lee et al., 2000). Although functional imaging experiments show that tonotopic organization exists within primary auditory cortex (Formisano et al., 2003), to our knowledge tonotopic auditory organization has not been demonstrated using microstimulation in human patients, perhaps because primary auditory cortex is smaller and less accessible than the other primary cortical areas.

Animal studies using electrodes that can both record neuronal response properties and microstimulate demonstrate a precise correspondence between neuronal properties and evoked movements or percepts. Microstimulating V1 in monkeys while presenting a small visual stimulus affects both the probability that the animal will make a saccade to that stimulus and the latency of the response (Tehovnik et al., 2002). These behavioral effects are restricted to the extent of the receptive fields of neurons at the site of stimulation (Tehovnik et al., 2004, 2005; reviewed by Tehovnik and Slocum, 2007), although the maximum precision of this correspondence is limited by the scatter in receptive field locations, approximately one-half a receptive field diameter (Hubel and Wiesel, 1962; Hetherington and Swindale, 1999).

In somatic motor cortex, distinct movements or muscle activations are routinely seen for stimulation sites separated by only a few hundred microns (Asanuma and Rosen, 1972; Donoghue and Wise, 1982; Neafsey et al., 1986). Microstimulation of the precentral cortex of monkeys produces stereotyped complex movements that resemble natural movements (e.g., reaching and grasping) when long stimulation trains (500–1000 ms) are used (Graziano et al., 2002). Prolonged stimulation of a given site produces a particular posture regardless of the starting posture or the particular muscles that must contract. Shorter stimulus trains do not allow complex movements to complete, but nevertheless can reveal the early components of coordinated postural adjustments (Graziano et al., 2004). However, in contrast to oculomotor and sensory areas, in primary motor cortex it has been difficult to relate the movements elicited by stimulation to the tuning of neurons that have been recorded in the same region of cortex (Strick, 2002; Aflalo and Graziano, 2006, 2007). Anatomically, the motor neurons that project to a given muscle are distributed over several millimeters, a larger distance than between stimulation sites that activate different muscles (Rathelot and Strick, 2006). It is thus still unknown how the tuning properties of neurons in primary motor cortex relate to the movements evoked by stimulation. Few studies of motor cortex have used low currents to perturb or bias natural movements. Such subthreshold stimulation might be interpreted more naturally by the brain.

3.2. Microstimulation of extrastriate visual areas

Stimulation of the primary cortical areas suggests that the experience produced by activating neurons closely follows the experience produced by the natural sensory stimuli or the natural movements that are most effective at activating neurons at the stimulation site. Experiments that use microstimulation in extra-striate visual cortex show that this principle also applies for neurons that represent more complex types of visual information.

The most comprehensive body of work relating microstimulation to changes in perception has come from Newsome and colleagues, who studied the behavioral effects of stimulating the middle temporal visual area (MT) in monkeys. Neurons in MT represent visual motion and respond selectively to specific directions and speeds (Maunsell and Van Essen, 1983a,b). Newsome and colleagues trained monkeys to do a direction-discrimination task in which they had to report whether the overall motion in a noisy dynamic random dot stimulus was stronger toward one direction or its opposite. They placed a microelectrode in MT where neurons preferred a particular direction of motion and aligned the visual stimulus so that its overall motion was in that direction or the opposite. They then measured the effect of

microstimulating those neurons on the animal's perceptual decisions when the stimulus to be discriminated contained only a weak motion stimulus. Microstimulation increased the probability that the animal would report seeing motion in the stimulated neurons' preferred direction, whether the actual motion was in that direction or the opposite (Salzman et al., 1992; Murasugi et al., 1993; Salzman and Newsome, 1994). This provided strong evidence that the firing of stimulated cells near the electrode directly contributed to judgments of motion direction.

Other experiments had monkeys detect near-threshold motion pulses and compared the effects of briefly presenting weak visual motion with the effects of briefly microstimulating MT (Masse and Cook, 2010). The two manipulations had similar effects on behavioral detection of motion. When MT is stimulated during the initiation of smooth pursuit of a moving target, animals generally respond with eye movements that are a vector average of the target movement and the motion preferred by the stimulated neurons (Groh et al., 1997), although stimulating MT sites where neurons preferentially signal "wide-field motion" rather than target motion can interfere with pursuit (Born et al., 2000). When monkeys are repeatedly exposed to microstimulation of MT during smooth pursuit eye movements, they adjust the direction of their smooth pursuit as they would to compensate for visual motion in the direction preferred by the stimulated neurons (Carey et al., 2005). All these experiments involving MT suggest that electrically stimulating neurons that respond selectively to a particular direction of motion produces percepts consistent with the presentation of a visual stimulus that moves in that direction.

MT neurons are sensitive to binocular disparity, in addition to direction of motion (Maunsell and Van Essen, 1983b). When monkeys judge the binocular disparity of moving stimuli, microstimulation of MT neurons biases their reports toward the binocular disparity that is preferred by the stimulated neurons (DeAngelis et al., 1998). However, stimulation of MT affects only absolute, not relative, disparity discriminations even though information for both exists in MT (Uka and DeAngelis, 2006). Because information about relative disparity is represented in several visual areas, this distinction highlights the idea that microstimulation effects may depend on the extent to which the stimulated neurons contribute to the task being performed.

Most sensory neurons in cortex are sensitive to multiple stimulus attributes (color, direction, size, etc.), and each will respond optimally to a specific combination of those attributes (Geisler and Albrecht, 1995). Although microstimulation studies typically examine effects on a single stimulus attribute that is prominently represented by the stimulated neurons, activating cortical neurons likely affects perception along multiple stimulus dimensions. Microstimulation therefore might bias perception toward the experience of the activated neurons' preferred stimulus, with the shift in perception weighted by the relative sensitivity of the neurons to the different attributes.

Neurons in MT send axonal projections to the medial superior temporal area (MST), which also contains many neurons that are directionally selective (Tanaka et al., 1986a). Microstimulation of sites in MST also affects motion discrimination (Celebrini and Newsome, 1995). Many MST neurons respond more strongly to patterns of optic flow, such as expansion or rotation, than they do to simple translation (Saito et al., 1986; Tanaka et al., 1986b; Duffy and Wurtz, 1991a,b). It has been suggested that this type of visual selectivity might be important for navigation. Consistent with this idea, microstimulation of MST neurons that are selective for optic flow can bias a monkey's assessment of its movement through a visual environment (Britten and van Wezel, 1998). Similar effects are seen in the ventral intraparietal area, VIP, and they are strongest when animals are making pursuit eye movements during the discrimination task (Zhang and Britten, 2011).

Late stages of visual cortex contain neurons with complex response properties, and inferotemporal cortex (IT) contains neurons that respond selectively to faces (see Tanaka, 1996; Logothetis and Sheinberg, 1996). Afraz et al., 2006 trained monkeys to do a task in which they had to report whether a noisy image was a face or some other object. They then microstimulated inferotemporal sites at which face-selective cells were concentrated. Stimulation increased the probability that the monkey would report that an image contained a face, and the effects were greatest for stimulation sites that were more selective for faces. Thus microstimulation can specifically affect the perception of complex objects.

3.3. Microstimulation of other cortical regions

As described above, behavioral effects have been demonstrated from microstimulation of neurons in areas that span visual cerebral cortex. This raises the possibility that microstimulation anywhere in cerebral cortex can alter the sensory, motor or cognitive state of the subject. However, the number of experiments demonstrating more complex effects from microstimulation remains limited. This can be attributed in part to a lack of understanding about how different cortical areas contribute to behavior. Microstimulating visual cortex typically yields modest shifts in behavioral performance using near-threshold stimuli. Effects have been demonstrated primarily in areas where the visual response properties are well characterized, and therefore a good guess can be made about what types of discriminations are likely to depend on the neurons in question. Microstimulation is unlikely to produce measureable behavioral effects if the task does not depend to a large extent on the stimulated neurons. Because a successful microstimulation experiment requires a reasonably thorough understanding of the properties of the stimulated neurons, most focus on areas that are robustly sensory or motor in character. However, some microstimulation experiments have succeeded in altering higher level aspects of task performance.

Microstimulation of the frontal eye fields (FEF) has long been used to produce saccadic eye movements (Ferrier, 1875), with different sites producing saccades with different directions and amplitudes (Robinson and Fuchs, 1969; Bruce et al., 1985; Knight and Fuchs, 2007). When monkeys do a task that requires them to move their gaze to one of two moving targets and then track it with pursuit eye movements, electrical stimulation of the FEF that brings gaze onto one target guides the pursuit eye movement system in the same way that self-generated saccades do (Gardner and Lisberger, 2002). In animals without head restraint, microstimulation of the FEF produces gaze shifts that combine eye and head movements in a manner similar to natural gaze shifts (Knight and Fuchs, 2007). Eye and head movements can also be produced by microstimulation of the nearby supplementary eye fields (SEF, Schlag and Schlag-Rey, 1987). Stimulation of the SEF produces head- and eye-mediated gaze shifts that are indistinguishable from natural gaze shifts, in that they obey the same kinematic rules as natural gaze shifts (Martinez-Trujillo et al., 2003). Microstimulation of the FEF versus the SEF has distinctly different effects on monkeys making remembered sequences of saccades. Microstimulation of the SEF, but not the FEF, selectively biases the sequences of saccades that animals make, but not the precision or other metrics of those eye movements (Histed and Miller, 2006). This result supports the idea that the SEF are involved in higher-level organization of sequences of movements (see Nachev et al., 2008). Microstimulating motor cortex for sufficiently long periods can evoke specific postural changes that differ systematically between sites, suggesting that motor cortex contains a map of the subject's "motor repertoire" (Graziano, 2006).

Microstimulation in some cortical areas can mimic the effects of spatial attention. Stimulating a site in the FEF with currents weaker than those needed to generate an eye movement can improve behavioral performance in a luminance decrement detection task, but only when the change to be detected is in the part of the visual field represented by the stimulated site (Moore and Fallah, 2001, 2004). Subthreshold microstimulation of the FEF

enhances a motion-induced position illusion, which is consistent with enhanced spatial attention rather than coding for a fixed saccadic vector (Schafer and Moore, 2007). Subthreshold microstimulation of the FEF modulates the visual responses of V4 neurons with receptive fields in the appropriate part of the visual field in a manner reminiscent of the modulation produced by spatial attention (Moore and Armstrong, 2003; Armstrong et al., 2006). Effects consistent with an increase of spatial attention are also seen with microstimulation of the monkey posterior parietal cortex (Cutrell and Marrocco, 2002) and superior colliculus (Muller et al., 2005; Cavanaugh et al., 2006).

3.4. Spatial and temporal precision of microstimulation effects

In addition to demonstrating specificity in the types of effect produced by different areas in cortex, microstimulation also provides insights about the spread of neuronal activity over cortical distance and time.

For example, although microstimulation of MT affects the perception of direction when the visual stimulus is aligned with the receptive fields of neurons at the stimulated site, positioning the stimulus just outside of the receptive fields of the stimulated MT neurons greatly reduces the effect (Newsome et al., 1990; Salzman et al., 1992). This result suggests that in this configuration, microstimulation does not affect the MT neurons that provide the most reliable signals about the visual stimulus, which are located about 1 mm away from the stimulation site (Maunsell and Van Essen, 1987).

Other observations suggest that the behavioral effects of microstimulation are predominantly restricted to a few cortical columns (a few hundred microns). Because the effects of microstimulation in monkey MT depend on the direction selectivity of the neurons around the electrode tip, they are likely to depend on the preferential activation of a limited number of the direction columns that exist in that area (Albright et al., 1984). Consistent with this, when neurons preferring one direction are stimulated while presenting a visual stimulus moving in another direction, monkeys report seeing an intermediate direction of motion (Nichols and Newsome, 2002). Additionally, moving the electrode a few hundred microns to a site with a different direction preference can eliminate or reverse the behavioral shift in reported direction when monkeys must discriminate between opposite directions of motion (Salzman et al., 1992; Murasugi et al., 1993). Similarly, the effects of V1 microstimulation on visual stimulus detection in monkeys are greatest when the stimulus is presented to the eye that dominates the neurons at the stimulation site, suggesting that microstimulation can preferentially affect neurons within one ocular dominance column (Slocum and Tehovnik, 2004). In monkey somatosensory cortex (area 3b), the ability to discriminate the frequency of electrical stimulation requires that the electrode be positioned among neurons that adapt quickly to somatosensory stimuli. Moving the electrode into a column of slowly adapting neurons degrades behavioral performance (Romo et al., 2000). These observations related to columnar organization suggest that typical microstimulation parameters have behavioral effects that reflect the properties of neurons lying within a few hundred microns of the electrode tip.

Differences in the effects of high- versus low-current stimulation support the role of columnar specificity in microstimulation effects. High-current stimulation should spread to affect more cortical columns, and several studies have reported loss of behavioral specificity with higher currents. Stimulating MT with currents well above the threshold for producing behavioral effects (80 μA) impairs direction discrimination, presumably because a more intense current activates neurons in cortical columns that prefer many different directions, causing a percept that has little or no direction specificity (Murasugi et al., 1993). Intracortical stimulation of V1 in humans leads to reports of phosphenes with highly saturated colors only when currents are near threshold (Schmidt et al., 1996). At higher

stimulus intensities phosphenes usually appear white, gray or yellow, presumably because stronger currents activate larger regions of cortex that include neurons preferring all colors.

The spatial specificity of microstimulation has also been shown in experiments that asked whether human patients could resolve the phosphenes produced by simultaneous intracortical microstimulation from two closely spaced microelectrodes. Subjects can typically resolve phosphenes produced by electrodes separated by as little as 500 μm (Bak et al., 1990; Schmidt et al., 1996). Other observations suggest that there is spatial specificity on the radial dimension of cortex as well. In particular, behavioral thresholds for affecting the timing of saccades with microstimulation differ between the superficial and deep layers in monkey V1 (Tehovnik et al., 2003).

In addition to spatial specificity, the effects of microstimulation are also precise in time. Applying MT microstimulation immediately before a motion stimulus has no effect on perceptual reports about the direction of stimulus motion (Salzman et al., 1992; Seidemann et al., 1998). Similarly, the behavioral enhancement seen with FEF stimulation during a spatial attention task is not observed if the microstimulation occurs more than a few hundred milliseconds after target onset (Moore and Fallah, 2004). The efficacy of stimulating the FEF with a given number of pulses in a short period (35 ms) varies with the temporal patterning of those pulses (Kimmel and Moore, 2007).

Collectively, these results suggest that the behavioral effects of microstimulation arise from a population of activated neurons that mostly lie within a few hundred microns from the electrode tip, as suggested by the two-photon calcium imaging of activated neurons described above (Histed et al., 2009). Although some directly activated neurons lie at greater distances from the electrode, behavioral effects appear to be determined by the majority of directly activated neurons that lie close to the tip. While directly activated neurons undoubtedly drive many more neurons indirectly, specific behavioral effects can be related to neurons near the electrode, implying that causal effects are mediated by the directly affected neurons.

3.5. Cortex as a place code

Collectively, microstimulation experiments in many cortical areas and behavioral tasks appear to have similar effects. In overtly sensory or motor areas, microstimulation causes percepts or movements that are closely related to the natural stimuli or motions that most strongly drive the stimulated neurons. Correspondingly, activation of neurons that represent task-related information perturbs behavioral states in predictable ways that bring them closer to the states that would normally be associated with the activity of those neurons. The brain appears to assimilate the artificial signals introduced by microstimulation and process them as if they were generated naturally. Indeed, it has been suggested that in some situations subjects cannot distinguish neuronal signals produced by near-threshold microstimulation from natural neuronal activity (Salzman et al., 1992).

These findings evoke the concept of a place coding of information in cerebral cortex (Groh, 2001; Graziano, 2006). Place coding refers to a fixed relationship between specific percepts and the activity of specific neurons, an idea that can be traced back to the law of specific nerve energies (Müller, 1833) and the concept of labeled lines (Helmholtz, 1867). While it has been strongly argued that no percept maps entirely onto the activity of an individual neuron (e.g., Erickson, 1968), the history of cortical neurophysiology has been one of establishing correlations between the activity of specific local populations of neurons and specific perceptual, motor or cognitive states. Microstimulation studies make it possible to attribute a specific perceptual, motor or cognitive state to the activation of neurons in a certain region.

The existence of a place code does not deny the possibility of more elaborate codes, such as codes that represent information in the precise patterning of the timing of activity in subsets of neurons (e.g., Gewaltig et al., 2001; Abeles, 1991) or in the timing of firing relative to oscillations in field potentials (e.g., Fries et al., 2007). While the cortex might additionally use more subtle information coding mechanisms, a place code representation of behaviorally relevant information appears to be a central component of cortical function.

4. Guiding behavior with microstimulation alone

4.1. Detecting and discriminating cortical microstimulation

Many of the experiments considered so far involved perturbations of the perception of a sensory stimulus, but for the remainder of this review we will discuss the detection and discrimination of microstimulation that is not combined with natural stimuli. The majority of studies describing behavioral reports about electrical stimulation alone have been carried out in the primary sensory or motor cortex. Patients describe phosphenes or other basic sensations when their primary sensory cortices are stimulated, and animals can be trained to report when their primary sensory cortices are stimulated (Bartlett and Doty, 1980; Tehovnik and Slocum, 2006; Murphey and Maunsell, 2007). When virus injections are used to make neurons in barrel cortex express channelrhodopsin (ChR2), mice can be trained to respond to optical activation of those neurons (Huber et al., 2008). Similarly, in mice with ChR2 widely expressed in cortex, optical stimulation can be used to map motor cortex (Ayling et al., 2009).

Animals can also be trained to discriminate which of two electrodes delivered a stimulus. Rats and gerbils with two electrodes chronically implanted in auditory cortex can learn to discriminate which electrode was stimulated, even when the electrodes are separated by as little as 1 mm (Otto et al., 2005; Deliano et al., 2009). Presumably the electrodes generate auditory percepts that are distinct to the animals, and the discrimination is made on this basis. Small timing differences can also be detected. Rats can detect differences as small as 3 ms in the onset of trains of microstimulation at two electrodes chronically implanted in auditory cortex (Yang et al., 2008).

In most experiments in which animals must detect cortical microstimulation, there is no effort made to understand what percept those animals experienced, but Romo and colleagues (2000) provided an important exception. They first trained monkeys to do a task in which two vibrating stimuli were sequentially delivered to a fingertip. To earn a reward, the animal had to report whether the first or second stimulus vibrated at a higher frequency. When vibrations were in the range of 10–40 Hz, the animals could reliably distinguish differences of a few Hertz. The investigators then inserted a microelectrode into the part of area 3b in primary somatosensory cortex that represents the fingers, and replaced one of the vibrating tactile stimuli with bursts of electrical pulses, with the burst frequencies varying from trial to trial. The monkeys' performance comparing electrical stimulus frequencies with tactile stimulus frequencies or electrical stimulus frequencies against each other was almost identical to performance using only tactile stimuli. Thus monkeys can readily discriminate small changes in the temporal parameters of the stimulus trains delivered to primary somatosensory cortex. Subsequent experiments have shown that monkeys can also discriminate frequencies of microstimulation in area 3a (London et al., 2008).

4.2. Thresholds for detecting cortical microstimulation

Several studies have shown that animal subjects can detect microstimulation not only in primary sensory areas, but also almost anywhere in cortex. In a series of experiments in the 1950s and 1960s, Doty and his colleagues trained cats and monkeys to respond when they detected cortical microstimulation (reviewed by Doty, 1969). Importantly, extended training

was necessary before animals could reliably detect microstimulation outside of primary sensory areas. We will discuss the importance of this training below; for this section, we will consider only behavior after training had been completed. In one study using well-trained monkeys, behavioral responses were obtained from stimulation in each of 38 sites that spanned all the lobes of cerebral cortex (Doty, 1965).

Because stronger stimulation currents directly excite more neurons, measuring the amount of current necessary for microstimulation detection makes it possible to explore whether there are regional differences in the number of cortical neurons that must be activated before a subject can detect their activity. Murphey and Maunsell (2007) trained monkeys to detect cortical microstimulation and compared current thresholds for detection in different visual areas in cortex. At each site, a detection threshold was determined by testing detection with a set of fixed currents (Fig. 1A). Using this approach, the authors tested many sites in different cortical areas. Following extensive training, they found remarkably little difference in thresholds across visual cortex (Fig. 1B). Median detection thresholds were about 6 μA for sites in V1. Thresholds increased somewhat in later stages of visual cortex, reaching a median of about 11 μA in inferotemporal cortex, but there was considerable overlap in the thresholds for all visual areas tested. Median thresholds for detecting microstimulation were only slightly higher in the FEF (14 μA), well below the level needed to evoke eye movements (Murphey and Maunsell, 2008).

A few studies have compared behavioral thresholds for detecting microstimulation of different layers of V1. Most have reported higher detection thresholds in the superficial layers of V1 in monkeys (Tehovnik et al., 2002; Murphey and Maunsell, 2007) and humans (Bak et al., 1990), but one study found the lowest thresholds in the superficial layers of monkey V1 (DeYoe et al., 2005). The difference may stem from the use of a yes-no task design in most experiments. With this design subjects can artificially elevate the thresholds measured for some stimuli if they are more conservative about responding to those stimuli. Subjects might become more conservative if a given stimulus (e.g., stimulation of either superficial or deep cortical layers) produces an unusual percept. A two interval forced-choice design largely avoids this problem (Green and Swets, 1966) and the one study that used forced-choice (Murphey and Maunsell, 2007) had thresholds with less variance between sites in V1 and found that thresholds were only slightly higher in the superficial layers (by ~20%).

4.3. The minimum detectable cortical activity

Monkeys can detect V1 stimulation with relatively weak currents. A median threshold of 6 μA (Murphey and Maunsell, 2007) is indistinguishable from the median threshold needed to produce a detectable two-photon calcium signal in cat or mouse V1 (Histed et al., 2009). This raises the question of what is the smallest behaviorally detectable unit of cortical activity. Subjects can detect activation of a single peripheral nerve fiber (Ochoa, 2010), but can they detect the activity of a single cortical neuron? Experiments in rats suggest that they can.

“Nanostimulation” is the technique of using a glass pipette in a juxtacellular configuration to either record intracellular potentials in a neuron or inject currents into it to depolarize its membrane to make it fire action potentials (see Houweling et al., 2010). This approach has revealed how influential one neuron can be (see Wolfe et al., 2010). Activation of an individual pyramidal neuron in rat motor cortex can produce whisker movements (Brecht et al., 2004; Herfst and Brecht, 2008). Remarkably, rats can detect the activation of individual neurons in barrel cortex (Houweling and Brecht, 2008). It remains to be seen whether this effect is special to the barrel field of rodents, or more generally applicable to primary sensory areas or all of cortex.

4.4. Cortex as a palette of information

Experiments that measure behavioral thresholds for detecting microstimulation suggest that no region of cortex is distinctly privileged with regard to producing spikes that can be detected and reported. It is conceivable that future testing will reveal some cortical areas where direct activation cannot be used to guide a behavioral response, but that seems unlikely given the consistent success in generating behavioral responses from the stimulation of cortical sites spanning all lobes of cortex. The results from studies of microstimulation detection suggest that neuronal signals in all parts of cortex are similarly accessible for guiding behavior.

In studies that measure thresholds for detection, no attempt has been made to assess what percepts animal subjects experience while detecting stimulation of different cortical areas. Based on the experiments described earlier, in which microstimulation perturbed percepts or behavioral states in specific ways depending on which neurons were stimulated, it seems likely that the microstimulation percept is dictated by the response properties of the stimulated neurons. Thus, while in some cases the animals may be reporting that they perceived a phosphene or other sensory experience, when they learn to report microstimulation of regions such as frontal cortex they might be responding to experiences that lack a pronounced sensory aspect, as with patients who receive cortical stimulation and report an urge to move (Fried et al., 1991) or sense the presence of another (Arzy et al., 2006).

As discussed earlier, findings from experiments in which microstimulation perturbed percepts or behavioral states suggested that there is a type of place code for cortical representations, with each site in cortex specialized to represent a different type of sensory, motor or cognitive information. Microstimulation alters the state of the subject in a way that maps directly onto the signals represented by the neurons in the stimulated cortical site. The findings from the detection experiments add the idea that the different types of information represented across the cortex are all accessible for guiding behavior. At any given moment, a subject might require sensory, motor or cognitive information that is most reliably represented by neurons that could be anywhere in cortex depending on the nature of the information. The detection experiments described here suggest that the brain can readily access signals in any part of cerebral cortex. In this sense, the cortex provides a palette of information, from which the brain can monitor or extract the signals most relevant to the task at hand.

5. Undetectable cortical signals

Until now we have only discussed successes in detecting the microstimulation of cortical sites spanning all parts of cortex. However, training is an important factor in achieving successful performance. Here, we consider the inability of subjects to detect stimulated cortical activity when they have not practiced detecting that stimulation.

When robust microstimulation is used to perturb a subject’s cortical activity, one might expect that the perturbation is readily evident to that subject. Remarkably, subjects are frequently unable to report even intense stimulation of sites in their cerebral cortex. Several lines of evidence suggest that this insensitivity is not a failure of instruction, attention or effort, but instead a genuine inability to register some types of cortical activity. Such failures to detect cortical signals provide important insights into the accessibility of signals in cortex.

5.1. Failing to detect cortical microstimulation

The ability of subjects to reliably detect electrical stimulation in some parts of cerebral cortex was well documented by Penfield and colleagues, who showed that stimulation of the

primary sensory and motor areas produces patent, modality-specific effects with a clear topographic organization. This finding has been supported by many animal studies that have documented behavioral responses to low-current intracortical stimulation of primary somatosensory (Butovas and Schwarz, 2007), auditory (Rousche and Normann, 1999) or visual cortex (Bartlett et al., 2005; DeYoe et al., 2005). What is less frequently emphasized about Penfield's results is that patients rarely detected stimulation outside the primary cortical areas and the immediately surrounding cortex. Fig. 2 summarizes sites described by Penfield and Rasmussen (1950) as evoking sensations or movements when stimulated electrically. Stimulation was most effective in and around the primary sensory and motor areas. The authors did not illustrate sites producing somatosensory percepts, but noted that these were rarely encountered at a distance greater than 1 cm from the central fissure (i.e., in the immediate vicinity of primary somatosensory cortex; see their p. 22). Over large swaths of cerebral cortex, no movements were observed and no percepts were reported in response to even vigorous stimulation of the cortical surface.

This failure to generate responses might seem inconsistent with experiments showing that animals can detect low-current stimulation throughout cortex. However, those animal experiments critically provided the subject extensive practice at detecting the stimulation (see below). A failure to detect microstimulation might also seem at odds with Penfield's often-cited "experiential hallucinations", in which subjects described vivid scenes or memories from their past when cortex in the temporal lobe was stimulated (Penfield, 1947). These elaborate experiences, together with the basic percepts and motions associated with stimulation of primary cortical areas, seem to suggest that stimulation anywhere in cortex caused subjects to experience something simple or complex, depending on where the stimulus was delivered. However, the sites generating experiential hallucinations, while fascinating, were rare, involving only 24 of 1132 cases. Most of these patients suffered from temporal lobe seizures and reported that the experience caused by electrical stimulation was similar to hallucinations they experienced immediately before their epileptic seizures (Penfield and Perot, 1963). Penfield suggested that recurring epileptic discharges conditioned neuronal connections so that electrical stimulation could activate them (Penfield, 1947, p. 341). Thus the rarely seen experiential hallucinations were probably associated with pathological cortex. Stimulation of most cortical sites was undetected.

The testing used by Penfield with human patients was necessarily limited, and it is appropriate to question whether his patients were adequately trained or instructed to report percepts that might be unnatural or unexpected. More recent work has confirmed these observations using stimulation through surface electrodes that are implanted for many days to monitor epilepsy, a situation that allows for more comprehensive testing. With this approach, Lee and colleagues (2000) found that stimulation of most sites in occipital, parietal and temporal cortex fails to generate any response. Using forced-choice testing in subjects well-trained on a detection task, it was shown that while patients readily detect stimulation from electrodes in or near V1, the probability of readily detecting robust stimulation drops rapidly with distance from V1 (Murphey et al., 2009).

It should be noted that stimulation is detected at some sites far from primary cortical areas without training. For example, stimulation of some sites in human extrastriate visual cortex produce a sensation of color, movement or complex shapes (Lee et al., 2000; Murphey et al., 2009). Cortical stimulation can sometimes produce a percept of a face (Puce et al., 1999), an urge to make a particular movement (Fried et al., 1991), or even the sense of an alien presence (Arzy et al., 2006). Nevertheless, it is striking that electrical stimulation of most cortical sites cannot be readily detected using currents that must activate hundreds or thousands of neurons.

5.2. Failing to detect atypical endogenous cortical activity

The auras or prodromes that are sometimes associated with migraines also support the idea that atypical cortical activity is not readily detected, because they suggest that only primary sensory areas contribute to these percepts. It is thought that the migraine aura is caused by a slowly progressing wave of neuronal and glial depolarization (cortical spreading depression, see Tfelt-Hansen, 2010). Lashley (1941) carefully mapped the progression of his own aura across his visual field and concluded that it reflected a wave of activity traveling across V1 at 3 mm per minute. Activation of V1 is also suggested by the way that the visual patterns generally respect the vertical meridian (which is represented at the border of V1) and because visual auras usually assume relatively simple scintillating patterns, with complex hallucinations rarely reported (Wilkinson, 2004).

While visual auras from migraines map well onto a wave of activity that slowly traverses V1, BOLD imaging during migraine auras reveals activity that spans many visual areas (Hadjikhani et al., 2001). A wave of spiking activity spreading across V1 would cause postsynaptic effects in other visual areas, including substantial subthreshold activity detectable with imaging (Logothetis, 2002). Transcranial magnetic stimulation has shown that extrastriate visual cortex is hyper-excitable in migraines (Battelli et al., 2002) and neuroimaging studies have observed spreading depression in visual cortex beyond V1 during migraines without auras (reviewed by Sanchez del Rio and Alvarez Linera, 2004). Because magnification of the visual field varies greatly between visual areas, a wave of activity progressing across cortex at a fixed speed would map to faster speeds in the visual field in areas with less magnification. However, a single speed is typically reported, which corresponds to the visual field representation in V1. Thus, the atypical activity associated with migraine auras, like the atypical activity from microstimulation, might be largely undetectable when it occurs beyond primary sensory areas (see Wilkinson, 2004).

5.3. Limits on cortical readout

The failure of subjects to readily detect activation of their cerebral cortex by microstimulation, especially in non-primary sensory areas, provides clues about how signals are processed and integrated in the brain. Although this insensitivity was initially interpreted as showing that some regions of cortex were silent and nonfunctional (see Devinsky, 2005), that notion is untenable given neurophysiological data and observations from many other approaches. Instead, it argues that the brain is initially unable to process arbitrary spatial and temporal distributions of active neurons in cortex. Presumably activity in some sets of neurons fails to propagate because the neurons involved lack an adequate degree of convergence to produce further activity that leads to a behavioral report.

How can we reconcile failure to detect microstimulation alone with the experiments in which microstimulation in conjunction with natural stimuli reliably alters behavioral performance? The ability of microstimulation to consistently change reports about natural stimuli does not imply that subjects are aware that they have been microstimulated. When a subject evaluates a natural stimulus using cortical neurons that have been perturbed by microstimulation, it is unsurprising that the evaluation is affected. However, there is no reason to expect that the subject can detect that the cortical neurons have been perturbed by microstimulation, and the results described in this section suggest that they usually cannot. While the onset of a natural stimulus will capture attention, the onset of neuronal spiking in cortex generally does not.

6. Learning to detect microstimulation

It is not clear why subjects should be insensitive to stimulation-induced activity in their cerebral cortex. Perhaps the best clue comes from experiments that show that when animals

are allowed to practice detecting microstimulation, they become sensitive to microstimulation anywhere in cortex. With practice, subjects can learn to detect weak stimulation in cortex where previously much stronger stimulation was undetected. Studies that have looked more directly at this plasticity suggest that some spatial and temporal distributions of local cortical activity are more easily accessed than others.

6.1. Physiological studies of microstimulation-induced plasticity

It should not be surprising that practice in detecting microstimulation can lead to improved behavioral thresholds. At the cellular and synaptic level, trains of electrical stimuli are commonly used to evoke long-term potentiation or long-term depression of neuronal connections in culture or slice experiments (Heusler et al., 2000). In vivo, there are many examples of microstimulation systematically altering the response properties of cortical neurons. Conditioning with extracellular currents that either increase or decrease the probability of cat V1 cells responding to specific stimuli alters the cells' selectivity in the direction of the stimulus that was artificially made more effective (Fregnac et al., 1988). The orientation map in cat V1 can be changed by microstimulation in anesthetized animals (Dinse et al., 1997; Godde et al., 2002), with an increase in the cortical area that represents the preferred orientation of the stimulated site. The somatotopic map in monkey area 3b can be changed by repeated microstimulation (Jenkins et al., 1990), and prolonged microstimulation at a site in somatosensory cortex results in cortical neurons up to a few hundred microns away becoming sensitive to the physical stimulation of the body surface represented at the stimulation site (Recanzone et al., 1992). Similarly, intracortical stimulation of bat auditory cortex can produce shifts in the best frequency of neurons (Ma and Suga, 2001). Consistent pairing of stimulation of one cortical site with the spiking of neurons in another cortical site has been show to enhance a measure of functional connectivity between the two sites in rat somatomotor cortex (Rebesco et al., 2010). Similarly, prolonged pairing of spiking at a site in monkey M1 with microstimulation of a different M1 site leads to changes in the movement associated with the unstimulated site, as if the stimulation enhances connectivity between the sites (Jackson et al., 2006).

6.2. Learning to detect V1 activity

Evidence of plasticity is also seen in behavioral experiments that require animals to detect microstimulation in isolation. The classic experiments by Doty and colleagues noted that thresholds in animal subjects improve with practice (Doty, 1969). Stimulation at sites all over cortex and in subcortical structures leads to detectable activity (Doty et al., 1956; Doty, 1965), but while a monkey generally responds immediately to a strong stimulus in V1, it "remains generally indifferent to stimulation in other cytoarchitectonic areas unless it is specifically trained to respond to stimulation there" (Bartlett and Doty, 1980). Recent work measuring rat behavioral thresholds for detecting microstimulation of somatomotor cortex have similarly shown that thresholds improve with practice (Rebesco and Miller, 2011).

The finding that cortical microstimulation can induce changes in neuronal response properties provides a ready explanation for why animals need extended practice before they can behaviorally detect microstimulation of most cortical sites: during the course of training neuronal connections change to support the detection of microstimulation (however, see Talwar and Gerstein, 2001, which reports the importance of the behavioral context of microstimulation-induced plasticity). The spatial and temporal distribution of activity produced by microstimulation is undoubtedly distinct from that which occurs naturally. Microstimulation will activate a sparse subset of neurons in the neighborhood of the electrode tip (Histed et al., 2009) more or less synchronously, while natural cortical activation can be expected to include neurons in all layers with different temporal relationships. Furthermore, some forms of microstimulation can produce robust inhibition

that is not seen with natural stimulation (Schiller and Malpeli, 1977; Logothetis et al., 2010). If some spatiotemporal distributions of spiking neurons are more effective at driving downstream circuits, then perhaps microstimulation before training fails to create patterns that can lead to propagating activity.

Detailed data showing that animals gradually improve their detection of microstimulation activity patterns have been provided by an experiment that tracked behavioral thresholds for detecting microstimulation of V1 in monkeys (Ni and Maunsell, 2010). Although untrained animals can easily detect strong V1 microstimulation, when the stimulation is relatively weak and near detection threshold, improvement can be seen over time. The example in Fig. 3A shows that a monkey initially could not detect trains of 50 μA stimulation in V1, although it was proficient at detecting small spots of light using the same task. With practice, detection thresholds improved with a roughly exponential time course and approached 6 μA after about 10 days – an improvement of at least 8-fold. This gradual improvement occurred even though the electrode was moved to a different site within a 3 mm × 3 mm region of V1 for each threshold measurement. The low thresholds plotted in Fig. 1 were from animals after they were fully practiced.

This improvement in detecting microstimulation shares three principal characteristics with perceptual learning of conventional sensory stimuli (Karni and Sagi, 1993; Goldstone, 1998; Tsodyks and Gilbert, 2004). First, performance improved incrementally over thousands of trials, as is seen with perceptual learning with natural stimuli (Schoups et al., 2001; Ghose et al., 2002; Yang and Maunsell, 2004). There is no indication of a sudden realization that responses should be guided by a particular sensation. Second, training was selective to the stimulated region. Thresholds improved only within the local 3 mm × 3 mm region of V1 that was microstimulated. After the data in Fig. 3A were collected, microstimulation was applied in a V1 region more than 10 mm from the trained region. As shown in Fig. 3B, while there was some generalization, thresholds were high and a new training session was needed to reach low thresholds. Monkeys that have been trained to discriminate different frequencies of microstimulation in one region of the somatosensory area 3a similarly perform at chance when sites a few millimeters away are stimulated (London et al., 2008). Third, the learning is long lasting, with thresholds remaining low over periods of up to a year with no intervening practice (gap in the data in Fig. 3B).

The fact that training with microstimulation detection is similar to perceptual learning with novel sensory stimuli suggests that cortex accommodates electrical microstimulation much as it does a new natural stimulus. Because stimulation in V1 is expected to produce a phosphene in a consistent place in the visual field and during learning the electrode is moved to different points in a 3 mm × 3 mm region of cortex, the improvement that occurs over tens of thousands of trials almost certainly is not based on the animal discovering what stimulus is associated with the reward. Instead, this gradual improvement suggests that subjects incrementally acquire the ability to perceive the stimulus, as with perceptual learning. Improvement in other cortical areas is similarly incremental (Murphey, Ni and Maunsell, unpublished observations) and is likely to similarly reflect a gradual learning process rather than a successful search for a suprathreshold stimulus. The ability to improve microstimulation detection in cortical areas outside of primary cortex supports the hypothesis that learning allows previously undetectable microstimulation to become detectable through cortical (or subcortical) plasticity.

6.3. The basis for learning to detect cortical activity

As monkeys are trained to detect V1 stimulation, they go from being insensitive to 25 μA stimuli to being able to detect 25 μA stimuli without fail (Fig. 3A and B). We do not know what neuronal changes underlie this improvement, but we can propose two possibilities.

First, detection might require a fixed number of active neurons in a local cortical region, and training on a detection task alters intrinsic neuronal properties so that a given electrical stimulus activates more neurons than it did originally. Alternatively, the number of neurons activated by the microstimulation does not change, but changes in inter-neuronal connectivity make the cortical circuit more sensitive to the spatiotemporal pattern of activation that is produced by microstimulation.

Several observations suggest that the neuronal changes associated with microstimulation involve specific changes in neural circuitry rather than an overall increase in neuronal excitability. Changes in rat behavioral thresholds for detecting cortical microstimulation are accompanied by changes in the functional connectivity between neurons in the region of stimulation (Rebesco and Miller, 2011). Additionally, expertise in detecting microstimulation is associated with profound, selective impairment on visual detection of natural stimuli that depends on the trained patch of V1. A local region of V1 corresponds to a small, well-defined portion of the visual field, so it is possible to measure how training on microstimulation detection of a local V1 region affects the ability to detect natural visual stimuli at the same location. Fig. 3C and D show thresholds for detecting small visual stimuli at the retinotopic positions represented by the microstimulated sites in Fig. 3A and B. After microstimulation training was complete, visual thresholds were elevated to ~5 times normal levels. These are substantial threshold elevations, comparable to motion discrimination impairments following ablation of MT (Newsome and Pare, 1988; Pasternak and Merigan, 1994). The effect was highly specific to the trained location: thresholds were normal for sites in the visual field only a few degrees away.

Several observations show that these elevated visual thresholds are not caused by damage from the electrical microstimulation or the associated microelectrode penetrations. Most notably, visual thresholds recover with practice following a time course of improvement that closely matches that for learning to detect electrical stimulation (Fig. 3C and D), and when visual thresholds recover, thresholds for detecting microstimulation are in turn elevated (Ni and Maunsell, 2010). The fact that non-invasive visual training elevates microstimulation thresholds suggests that the reciprocal relationship between visual and microstimulation thresholds does not reflect cortical damage.

This reciprocal relationship between thresholds for behavioral detection of visual and electrical stimulation of V1 suggests that learning does not involve a simple increase in the excitability of V1 neurons, which would raise sensitivity to stimulation of either type. Instead, it suggests that training involves changes in cortical circuitry that increase sensitivity to the specific spatiotemporal patterns of neuronal spiking associated with visual and electrical stimuli, which presumably differ considerably.

6.4. Why do primary areas support detection of microstimulation without training?

The notion that the brain is predisposed to process particular spatiotemporal patterns of activity from each cortical region suggests a tentative explanation for the efficacy of microstimulation of primary sensory and motor cortex. The punctate spatial distribution of active neurons produced around the tip of a stimulating electrode might not differ greatly from the distribution produced in the primary sensory cortices by a punctate natural stimulus, such as a point of light, a point of skin contact, or a pure tone. The activity produced by electrical stimulation may therefore be sufficiently close to a spatial pattern produced by natural stimuli such that large enough currents are processed with minimal training, leading to a modality-appropriate percept.

In contrast, it seems unlikely that any natural stimulus activates an isolated group of neurons in other cortical regions. Activity in regions beyond the primary sensory cortices is normally

accompanied by activity in the primary sensory cortex. Moreover, it is not clear that punctate activity ever occurs within some cortical areas. In visual cortex, for example, receptive fields grow increasingly larger and topographic organization becomes increasingly disorderly in successive areas. While columnar organization for different shapes exists in inferotemporal cortex (Tanaka, 1997), optical imaging experiments suggest that even simple stimuli are represented in widely distributed sites in that region (Wang et al., 1998; Tsunoda et al., 2001). In cortex beyond the primary areas punctate activation of a large number of neurons might not approximate any sort of natural pattern of activation, and might therefore fail to propagate in a way that can lead to a behavioral report in the absence of training-induced cortical plasticity.

6.5. Implications for cortical readout

The suggestion that only particular spatiotemporal patterns of neuronal activity can be used to guide behavioral reports has important implications for cortical readout. In principle, the activity of the billions of neurons in cortex could collectively represent an essentially infinite number of states. However, it has been suggested that the number of meaningful states of cortical activity is limited, with most of the possible states of neuronal activity in cortex mapping onto a much smaller set of meaningful states (e.g., Kanerva, 1988). The failure of most cortical stimulation to generate a response in untrained subjects suggests that many patterns of cortical activity are not efficacious and cannot be interpreted by other brain circuits. The fact that training to use a cortical site for detecting weak microstimulation impairs detection of natural stimuli, and vice versa (Ni and Maunsell, 2010), suggests that each local region of cortex can only be optimized to detect a particular pattern of activity – or class of activity – at any one time. Thus the modes of cortical activity that can actually be optimized for guiding behavior may be far more limited than suggested by the raw number of neurons in cortex.

6.6. Implications for neural prosthetics

The ability to learn to detect electrical activation anywhere in cortex has implications for the development of cortical sensory prosthetics. There has been considerable interest in the idea of using stimulation of central visual structures to restore some sensory function in blind individuals (reviewed by Tehovnik et al., 2009; Pezaris and Eskandar, 2009; Merabet et al., 2005). These efforts focus on stimulating V1 or earlier visual structures, which contain precise retinotopic maps of the visual field, with the hope of stimulating many sites, each of which provides a phosphene that serves as a pixel in an overall image (see Chen et al., 2009; Schiller and Tehovnik, 2008). This approach is challenging, because most of V1 is buried in inaccessible sulci on the medial wall of the hemisphere.

The potential for extensive plasticity in the interpretation of electrical activation of cortex is not frequently considered. We do not know what animals perceive when they learn to detect microstimulation of cerebral cortex. While it is possible that each site rigidly produces the percept associated with the natural stimulus that was most effective in driving its neurons, cortical sites might take on new meaning with training. This is suggested both by the new meanings that are assigned to sites in somatosensory cortex following amputation of a limb (Ramachandran, 2005), and by the rapidity with which subjects using a tactile visual prosthetic report that the somatosensory quality of the prosthetic becomes transparent as they externalize the signals (Segond et al., 2005). Blindness effectively deafferents large expanses of superficial extrastriate cortex, which might be a useful target for either pixel-based or processed visual signals.

7. Summary and conclusions

7.1. Insights from microstimulation

Microstimulation experiments have contributed many insights about the way that information is represented in and read out of cerebral cortex. Microstimulation has extended a vast body of neurophysiological recording data about differences between the types of information represented in various regions of cortex by showing that neurons with specialized response properties contribute in a causal way to specific behaviors. Experiments involving detection of microstimulation in different parts of cortex suggest that activity of neurons in all parts of cortex can be accessed to guide behavior. Because detection thresholds are relatively invariant from region to region, activity of a relatively constant number of neurons might be needed in any part of cortex to produce a response. Finally, experiments tracking behavioral thresholds for detecting microstimulation show that the adult brain retains considerable plasticity for learning to work with novel patterns of neuronal activity. The reciprocal relationship between thresholds for detecting visual and electrical stimulation of V1 suggests that there may be substantial limits to the number or range of patterns of activity that a local region of cortex can support.

These insights emphasize the power of microstimulation and related techniques as tools for exploring brain function. Causal relationships between neuronal activity and perceptual or cognitive states are difficult to establish without perturbing activity. Questions about whether signals in different parts of cortex can guide behavior cannot be addressed with natural stimuli or movements because any natural stimulus or movement will activate thousands or millions of neurons distributed across many cortical areas, making it impossible to attribute consequences to any specific neurons. With microstimulation, however, the experimenter can determine precisely where and when the relevant signals appear in cortex.

7.2. The promise of optogenetics

The development of methods for making neurons photosensitive offers the promise for sophisticated and powerful stimulation experiments that could not be achieved with electrical stimulation (Fenno et al., 2011; Yizhar et al., 2011). In particular, this approach makes it possible to selectively stimulate specific subtypes of neurons, such as those expressing a particular gene, or those that send axons to a particular target. This will make it possible to differentiate the contributions of different cells and structures to specific perceptual or behavioral capabilities. Optical methods can also be used to specifically inhibit or silence neurons, which cannot be achieved with electrical stimulation. Optogenetic stimulation can also produce spiking that is less synchronous than that caused by pulses of electricity, and therefore might be more natural (Berndt et al., 2009). Another important advantage of optogenetics is that it provides the possibility of controlling the subcellular site at which neurons are stimulated via genetic targeting to different cellular compartments (Grubb and Burrone, 2010). Optogenetic stimulation with ChR2 can generate spikes originating in the axon, soma, or dendrites under different conditions (Petreanu et al., 2007). While the axonal light threshold might be lowest for a small light spot, as with electrical stimulation, diffuse illumination can generate large currents from many parts of the dendritic tree (Wang et al., 2007; Huber et al., 2008) resulting in a more typical spike-initiation zone.

In some realms, however, electrical stimulation remains superior to optogenetics. In particular, it is straightforward to control the amount and density of charge transferred using electrical stimulation. This is more difficult with optogenetics, where the amount of protein expressed can depend on the efficiency of infection and can vary over time. Moreover, the number of photons delivered to different neurons can depend on aspects of light delivery

that are difficult to control precisely. Electrical stimulation can also perform better when high-frequency stimulation is needed. While improved ChR2 variants can produce spiking at higher rates (Lin et al., 2009; Gunaydin et al., 2010), precise spike timing at moderate frequencies requires high expression levels and intense light (e.g., Gunaydin et al., 2010). Finally, the genetic tools for optogenetics are most fully developed in mice and invertebrates, although it is likely that powerful tools will soon be available in other mammalian species (Diester et al., 2011).

7.3. Closing comments

Collectively, the results from microstimulation experiments suggest that the brain works with signals introduced into cortex by microstimulation in much the same way that it does with natural activity. There are many promising directions that remain to be explored.

For example, relatively little work has used microstimulation to explore the brain's spatial and temporal limits for processing neuronal signals. When eye movements are generated in the FEF, trains of pulses that accelerate in frequency are more effective than otherwise equivalent fixed-frequency trains (Kimmel and Moore, 2007). The ability of the brain to distinguish different frequencies and patterns of neuronal activity has not been systematically explored. The work of Romo and his colleagues (Romo et al., 2000) shows that monkeys can discriminate different frequencies of electrical stimulation in primary somatosensory cortex, but it is unknown whether this ability is unique to somatosensory cortex or primary sensory areas. Given current interest in the importance of the timing of neuronal activity, it would be valuable to know what temporal modulations of neuronal activity can be detected and discriminated in different regions of cortex.

In the spatial domain, much emphasis is placed on the need to bind together signals in different parts of cortex (Singer and Gray, 1995; Gray, 1999). Microstimulation can be used to explore limits on the integration of signals occurring at known sites in cortex (Ghose and Maunsell, 2010) and has the potential for addressing questions about spatially segregated cortical representations that could not be approached using other techniques.

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Abbreviations

BOLD	blood oxygenation level dependent
ChR2	ChannelRhodopsin-2
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
IT	inferotemporal cortex
MST	medial superior temporal area
MT	middle temporal visual area
VIP	ventral intraparietal area
VSD	voltage sensitive dye

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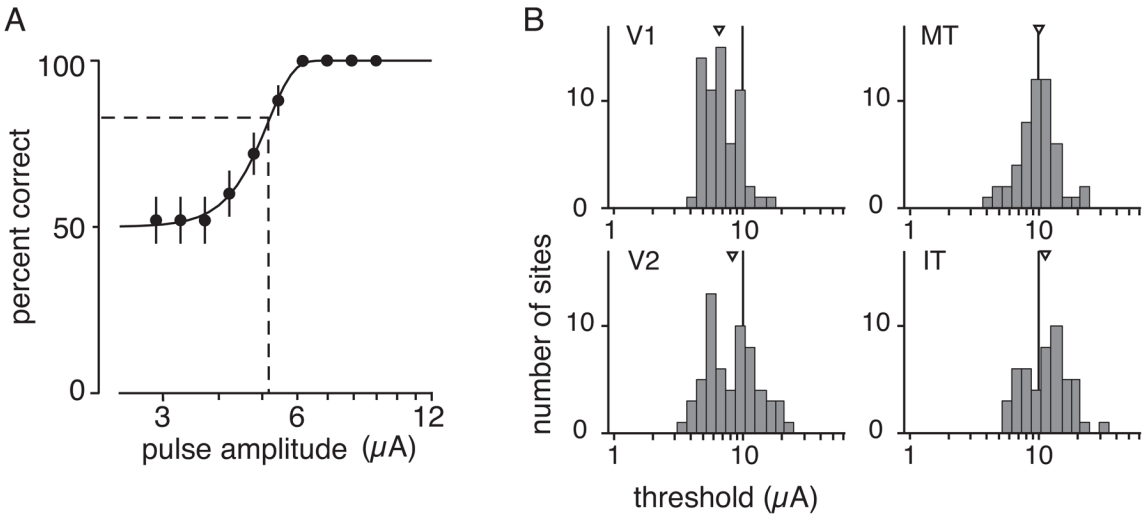

Fig. 1.

Distributions of detection thresholds. Thresholds for detecting electrical microstimulation delivered by a microelectrode in visual cortex. (A) Representative psychometric detection function for a V1 site. Threshold (5 μA) was taken as the current yielding 82% correct, where 50% represents chance. Error bars are SEM. (B) Distributions of detection thresholds for sites in different visual areas. Triangles mark medians. There was relatively little variance in thresholds within and between visual areas.

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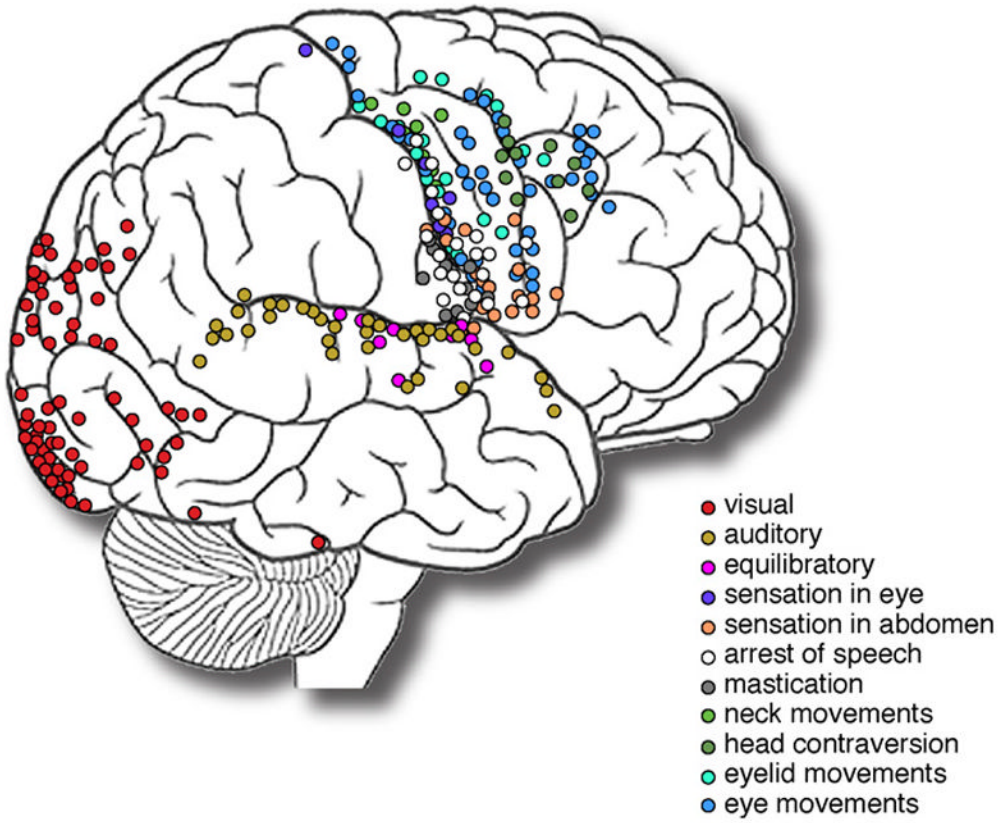

Fig. 2.

Penfield stimulation sites. Effects from stimulating human cerebral cortex. This figure summarizes effects reported by Penfield and Rasmussen (1950) in testing many patients. Points of different color mark the approximate locations where different patient responses were evoked, as indicated by the key. The authors did not plot the locations of somatosensory reports, so those data are not shown. Most responses were obtained in or around primary sensory or motor cortex, and large regions of cortex did not reliably produce movements or percepts.

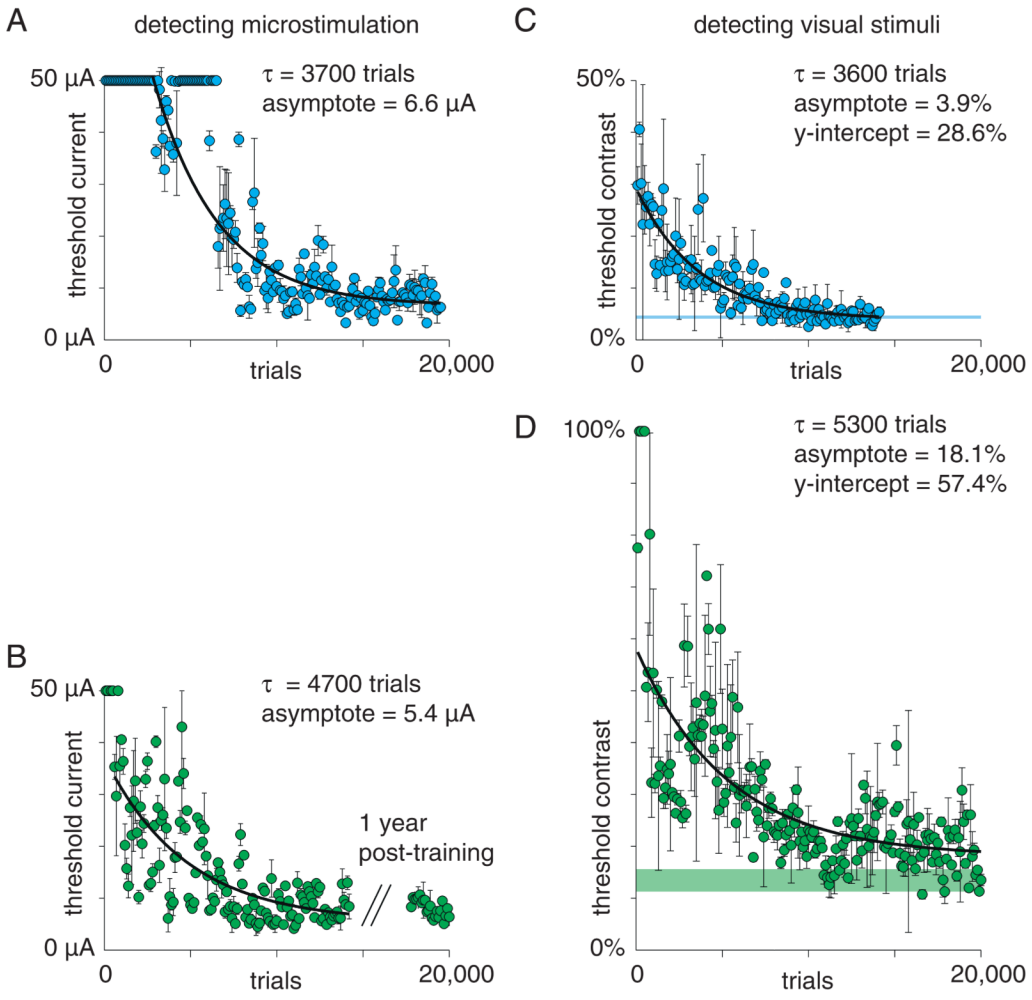

Fig. 3.

V1 Microstimulation training. Effects of training to detect microstimulation of V1. (A) Threshold current needed for behavioral detection of electrical stimulation of a small V1 region as a function of time. The monkey initially could not detect 50 µA stimulation, but thresholds gradually improved and stabilized near 6 µA over the course of many days when sites in a 3 mm × 3 mm region of V1 were tested. (B) Training was local and long lasting. After training the site in A, electrical stimulation at a distant V1 site required retraining to achieve low thresholds. Once trained, the effects were permanent. Thresholds were stable for over a year without further training at this site. (C) Training to detect electrical stimulation at the site in A impaired detection of visual targets. When visual stimuli were placed at the corresponding retinal location, thresholds were far above the normal range (which is marked by the thin horizontal band), but gradually returned to normal when the animal practiced detecting those visual stimuli. (D) Retraining with visual stimuli at the site in A and C did not improve visual detection at other sites. Visual thresholds were elevated for the site in B (initially the animal could not see stimuli of 100% contrast), but also improved when the animal practiced with visual stimuli in that retinal location. The horizontal band marks the range of normal visual thresholds for this site. Reproduced with permission from Ni and Maunsell (2010).