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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.

Contents

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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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.

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