Microcircuits for Attention

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Researchers who study the neuronal basis of cognition face a paradox. If they extract the brain, its cognitive functions cannot be assessed. On the other hand, the brain's microcircuits are difficult to study in the intact animal. In this issue of *Neuron*, Mitchell et al. make use of a promising approach based on waveform analysis to reveal new details about neuronal interactions during visual attention.

To study neuronal activity, neurophysiologists rely on two major approaches. One involves removing neurons from animals. With such in vitro methods as slices and cell cultures, living neurons may be manipulated and extensively characterized. The other approach is to keep neurons inside animals. In vivo preparations optimize the normal functionality of neurons but hinder visualization of them. Both types of experiments have been profoundly useful, yet perhaps we could ask for even more. Is it possible to characterize neurons thoroughly while maintaining them in behaving animals? If so, is it worth the trouble?

Evaluating the myriad properties of single neurons as they function in the intact brain is a challenge, but some laboratories are working toward this goal. It seems not only worth the trouble but imperative for understanding the circuit basis of behavior. More and more we are seeing new approaches in which in vitro concepts are applied to in vivo recordings. A paper by Mitchell et al. (2007) in this issue of *Neuron* provides an example of how a hybrid approach may be accomplished and why it is important.

Mitchell et al. (2007) are in vivo neurophysiologists; they study neurons that are hidden from view in the brains of behaving rhesus monkeys. A daily experiment in their laboratory would proceed as follows: a monkey performs a task similar to three-card monte that demands careful visual attention. Simultaneously, the investigator advances a microelectrode into the cerebral cortex and records the voltage along the way. The investigator sees neither the electrode tip nor any neurons. But when the electrode tip nears a neuron, changes are detected in the extracellular voltage because of the neuron's action potentials. These voltage changes are observed on an oscilloscope and constitute the action potential's "waveform." If the investigator can keep the waveform stable for the next hour or so while the monkey continues its task, attentional modulation of the neuron can be analyzed.

The end result of an experiment such as this is to establish how a neuron's firing rate correlates with task performance. This quantifies a neuron's signals but says little about its morphological identity or its place in larger networks. Unresolved is whether the neuron's influence is excitatory or inhibitory, or whether it projects locally or distally. To an extent one can hazard a guess at the answers by estimating the laminar position of the neuron and consulting anatomical studies of the area. But Mitchell and colleagues went further by analyzing the one explicit attribute of the neuron available to them: its action potential waveform.

Even in early in vivo neurophysiological studies, it was noticed that not all action potential waveforms are created equal (Mountcastle et al., 1969; Simons, 1978; Swadlow, 1989). One difference is in waveform width. In vitro work confirmed the width variability and provided an explanation for it (McCormick et al., 1985; Connors and Gutnick, 1990; González-Burgos et al., 2005). Some neurons have relatively narrow waveforms (Figure 1A, left). Intracellular analyses showed that, for the most part, their influence is inhibitory (Figure 1A, second from left). Other neurons have wider waveforms (Figure 1B, left). They are mostly excitatory and typically pyramidal in morphology (Figure 1B, second from left). Action potential waveforms therefore contain information about the functional action of a neuron, which in turn constrains the possibilities about where a neuron projects. In cerebral cortex, all inhibitory connections are local (Figure 1A, second from right), but excitatory neurons can project long distances (Figure 1B, second from right). A few previous studies used these principles to provide evidence that neurons recorded *extracellularly* in the behaving monkey may be classified as inhibitory or excitatory (e.g., Constantinidis and Goldman-Rakic, 2002; Rao et al., 1999; see also Barthó et al., 2004, and Swadlow, 2003). Waveform analysis therefore seems to offer a long-sought window on microcircuits in the awake, behaving primate brain.

The major contribution of Mitchell et al. (2007) was to apply this analysis to attentional research. Visual attention is the sensory process of focusing on one aspect of a scene at the exclusion of others. Attention may be directed at a particular feature (e.g., things that are green) or a particular location (e.g., things off to the right). Area V4 in visual cortex is well known to be particularly crucial for visual attention. Feedback from frontal cortex is known to influence V4 neurons (Armstrong et al., 2006), but beyond that, little is understood about how V4 interacts with the

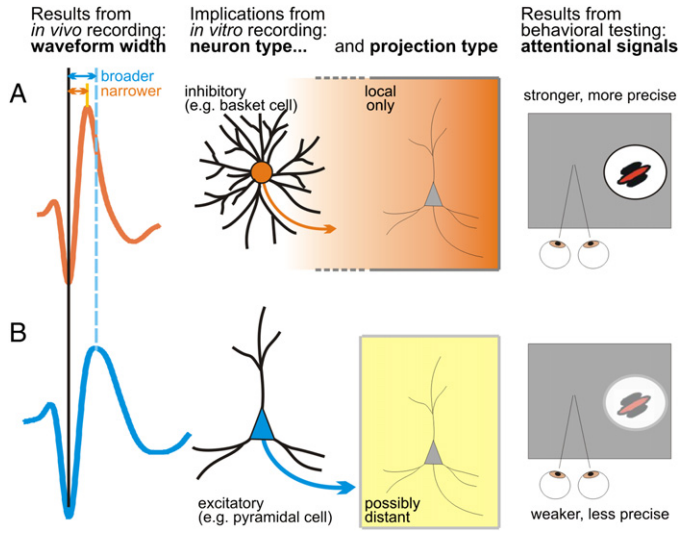

Figure 1. Experimental Diagram
(A and B) Conceptual diagram of the experiment by Mitchell et al. (2007). Waveforms are courtesy of S.-Y. Shin (MAS laboratory).

rest of the brain. Even such a fundamental circuit-level issue as whether attentional signals are carried by excitatory neurons, inhibitory neurons, or both has been unknown.

The first step of Mitchell et al. (2007) was to examine whether action potential waveforms of V4 neurons formed a bimodal distribution of widths. As predicted, a cluster of widths was found that was distinctly narrower than the rest. The narrow waveforms were from putative inhibitory neurons, and the wider waveforms were from putative excitatory neurons. The next step was to analyze whether these two classes of neurons had differing attentional modulation. This too was confirmed: putative inhibitory neurons had a larger change in firing rate, and a less variant change, during visual attention (Figure 1A, right) compared with putative excitatory neurons (Figure 1B, right). From this result Mitchell et al. (2007) concluded that inhibitory neurons play a particularly important role in visual attention. This supports models of attention that posit local competition between visual objects within neuronal receptive fields. It seems to provide less support for models of attention that emphasize long-range influences of V4 on the rest of the brain.

Some caveats should be noted, however. First, although putative inhibitory neurons were in some ways more modulated by attention than putative excitatory neurons, this is not to say that the latter were unmodulated. As a percentage of baseline visual activity, attentional modulation in both classes of neurons was comparable. Hence, although the authors emphasize the rather surprising role of local inhibitory circuits, long-range excitatory transmission of attentional information is likely as well. Second, as the authors noted, analysis of waveform width has its limitations. Some ambiguity arises because neurons have more than two phenotypes. To address this, Mitchell et al. (2007) performed further analyses using firing rate statistics and did find evidence for a third, albeit rare, class of neurons. While these caveats are important to keep in mind, they do not affect the main results of the study.

The waveform analysis used by Mitchell et al. (2007) is not the only way to characterize neurons in vivo. Other laboratories are using approaches that visualize neurons directly and confirm their circuit connections electrophysiologically. Direct visualization of neurons has been accomplished with optical imaging methods such as two-photon imaging in conjunction with calcium indicators (Ohki et al., 2005). Large populations of neurons can be seen, and light emission related to calcium release may indicate action potential generation. Also, circuit connections may be established with the classic techniques of antidromic and orthodromic stimulation (e.g., Lipski, 1981; Sommer and Wurtz, 2004). These methods involve recording a neuron in one area while a brief pulse of current is applied to a distant area. Stimulation-triggered activation of the neuron implies that it projects to, or receives input from, the distant site (specific tests can distinguish between the two possibilities).

Many questions for future work remain. First, can *subclasses* of excitatory and inhibitory neurons be characterized in V4 of behaving monkeys? As more information becomes available about the waveform signatures of different types of neurons, it may be possible to infer the underlying circuits in even more detail. Second, is it possible to watch entire populations of V4 neurons interact in vivo, to better understand the interplay between inhibitory and excitatory neurons during attention? Much of V4 lies on the surface of the brain, making it accessible to large-scale recordings through optical imaging or microelectrode arrays. Finally, can the interaction of V4 with other structures be determined in more detail? Antidromic stimulation studies could reveal the exact nature of attentional signals that enter or leave V4.

Elucidating microcircuits for cognition is an ambitious goal. Neurophysiologists are advancing toward it by combining the best attributes of two methodological worlds: the characterization methods inspired by in vitro studies and the behavioral testing opportunities provided by in vivo preparations. The report of Mitchell et al. (2007) provides an encouraging example of the feasibility and utility of inferring neuronal identity in primate brain research.

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Parkinson's Disease: Return of an Old Prime Suspect

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Pacemaking activity in adult substantia nigra (SN) dopamine neurons relies on L-type Ca^{2+} channels, but a surprising study in *Nature* by Chan et al. demonstrates that blockade of these channels by dihydropyridines re-establishes the pacemaking driven by sodium and HCN channels found in juvenile SN. This shift protects SN neurons in chemical models of Parkinson's disease (PD), suggesting that elevated intracellular Ca^{2+} participates in SN cell loss and that dihydropyridines may provide therapy in PD.

Parkinson's disease (PD) is diagnosed by a set of voluntary motor control dysfunctions known as "parkinsonism" that are due to the death of substantia nigra (SN) dopamine (DA) neurons and can be alleviated by DA replacement therapy using L-DOPA (Dauer and Przedborski, 2003; Sulzer, 2007). A major question is why certain neurons are targeted, and particularly why SN neurons die while neighboring midbrain DA neurons of the ventral tegmental area (VTA) are relatively spared (Damier et al., 1999).

A clue is provided by the unusual physiological properties of adult ventral midbrain DA neurons, which exhibit pacemaker activity in the absence of excitatory input (Grace and Onn, 1989), a feature widely suspected to underlie normal voluntary motor control, although there is at present little proof of that conjecture. Pacemaking in SN DA neurons depends on somatodendritic L-type channel-driven Ca^{2+} currents (Nedergaard et al., 1993) and to some extent or in some subpopulations on hyperpolarization-activated and cyclic nucleotide-gated cation (HCN) channels (Mercuri et al., 1995; Neuhoff et al., 2002) together with Ca^{2+}-activated SK K^+ channels that produce an afterhyperpolarization that delays return to threshold (Nedergaard et al., 1993).

The Ca^{2+} flux that underlies SN pacemaking is large, and midbrain DA neurons are to date unique in possessing a greater interspike calcium current than sodium current (Puopolo et al., 2007). Together with high Ca^{2+} flux that occurs during their relatively wide action potentials and presumed additional current when the neurons burst fire with excitatory input (Kuznetsov et al., 2006), normal SN neuron activity seems to entail unusually high Ca^{2+} entry.

In a new study published in *Nature*, James Surmeier's group at Northwestern University reports several surprising features of this pacemaking activity (Chan et al., 2007). First, pacemaking is already present in newborn mouse SN neurons but is driven by sodium channels in conjunction with HCN channels. Then, during the second week following birth, there is a gradual switch as $Ca_v1.3$ current increases, perhaps as the voltage dependence of HCN channels is shifted toward more negative membrane potentials, essentially taking HCN channels "off-line." The development of SN Ca^{2+}-driven pacemaking occurs in tandem with an increased expression of slowly inactivating somatodendritic L-type Ca^{2+} channels that drive the neurons into oscillations, due to the presence of