Shedding light on learning

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Brain-computer interfaces (BCIs) and optical imaging have both undergone impressive technological growth in recent years. A study in which mice learn to modulate neural activity merges these technologies to investigate the neural basis of BCI learning with unprecedented spatial detail.

Imagine the brain as a football stadium, with the fans as neurons. Learning a new behavioral task requires the neurons to produce new, coordinated activity patterns. This is analogous to the fans learning to hold up flashcards in a coordinated way to spell out a team's name. As with a fan trying to determine whether to hold up his or her flashcard on the basis of a low-resolution, aerial shot of the stadium shown on its jumbo screen, an individual neuron typically does not receive direct feedback about how its activity influences task success. How do the neurons (or fans) learn to coordinate their activity to produce the correct behavior? A study by Clancy *et al.*[1] in this issue unites two fast-growing technologies to examine the neural basis of learning: optical imaging, which can be used to record simultaneously from populations of individual neurons at high spatial resolution, and BCIs, which provide a closed-loop system for conditioning neurons to show particular activity patterns. This is the first time a BCI has been driven by optical signals and it provides new insight into how neurons change their activity during learning on a fine spatial scale.

Most BCI systems rely on electrical recordings. Typical intracortical electrodes sample neurons sparsely in a given brain area. Although it is possible to record from a small number of neurons on the same electrode, it is difficult to place the electrodes closely enough together to densely sample a local population. It is akin to dropping microphones into the football stadium: one can listen in on a few fans per seating section and, from that information, try to infer how the fans are learning the task. With optical imaging, however, one can listen to most of the fans sitting in a seating section[2]. Clancy *et al.*[1] used two-photon microscopy of an intracellular calcium indicator to track the activity of individual neurons via changes in fluorescence. With the proper microscope configuration, it is possible to record simultaneously from most neurons in the microscope's field of view.

Clancy *et al.*[1] exploited this novel combination of optical imaging and BCI to study learning in mice (**Fig. 1a**). By converting the fluorescence intensity to the pitch of an auditory tone, they conditioned the mouse to volitionally modulate a subset of the imaged neurons (termed direct neurons) to increase or decrease their activity[3]. At the same time, they also monitored many surrounding neurons (termed indirect neurons) that were not being conditioned[4]. The key innovation of the study was the ability to track the activity of neighboring, indirect neurons (in our stadium analogy, the surrounding fans) as the mouse learned to produce desired changes in tone pitch, at an unprecedented spatial resolution of tens of micrometers.

The authors found that the indirect neurons, which had no bearing on task success, initially tended to positively covary with the neighboring direct neurons (**Fig. 1b**). This effect was distance dependent, growing weaker the further the indirect neuron was from the direct neuron. This correlation between indirect and direct neurons was markedly localized, fading to near zero within 100 µm, which would have made it difficult to detect with extracellular electrodes. Perhaps more surprisingly, over the course of an experimental session (roughly tens of minutes), the average correlation decreased (**Fig. 1b**). One possible interpretation is that the mouse was able to identify and selectively modulate just those neurons responsible for task performance (that is, the direct neurons), even though the animal could have just as well continued to modulate the indirect neurons. Another possibility is that the animal found a strategy in which the indirect neurons were still modulated in a task-dependent manner, but in which some indirect neurons positively covaried and others negatively covaried with the direct neurons. Under either interpretation, it is clear from this study that there are distance-dependent changes in neural activity during learning that can be resolved using optical imaging but would be difficult to resolve using electrode recordings.

BCIs are best known for their rehabilitation benefits, in contexts in which neural activity is translated into control signals for a computer cursor or prosthetic limb to help paralyzed patients regain movement[5,6]. What has received less attention but is becoming increasingly recognized is the utility of BCIs for addressing basic scientific questions. A key advantage of BCIs for learning studies is that the full mapping from neural activity to behavioral output (for example, tone pitch, cursor movement or limb movement) is known and defined by the experimenter. In other words, BCIs allow the experimenter to specify task requirements directly on the neurons. By altering the mapping and monitoring the neural activity as the subject learns the new mapping, one can directly assess how the observed changes in neural activity relate to task requirements[3,4,7,8]. This provides a complementary approach to studying learning of more natural behaviors, where the mapping is not fully known[9]. With recent studies demonstrating high-performance cursor control using motor cortical activity[8,10], it is now possible to perform well-controlled basic scientific studies using BCIs. Indeed, BCIs are providing important insight into the neural basis of motor control and learning[3,4,7,8,11,12].

By linking BCIs with optical imaging, Clancy *et al.*[1] have developed a powerful tool

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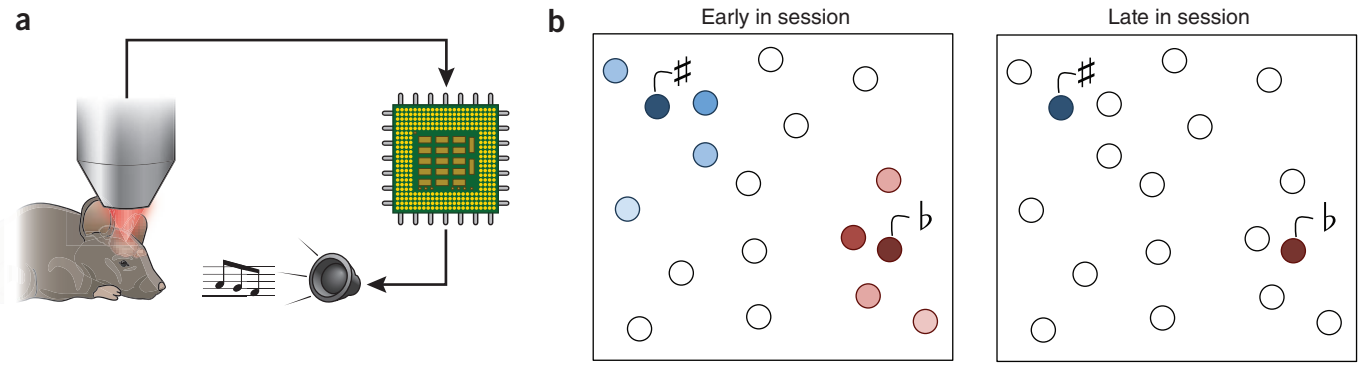

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Figure 1 Studying learning using an optical BCI. (**a**) Schematic of the closed-loop BCI system. Neural activity, measured by optical imaging of an intracellular calcium indicator, is converted in real time to auditory feedback (tone pitch). A mouse is trained to modulate neural activity to attain a specified pitch level for reward. (**b**) In a basic version of this task, the pitch is directly related to the activity of one neuron (♯, dark blue) minus the activity of another neuron (♭, dark red), together referred to as the direct neurons. Box indicates field of view of two-photon microscope; each circle represents a neuron. Initially, the nearby indirect neurons (light blue and light red) change their activity together with the direct neurons in a distance-dependent manner (left). Over the course of a few tens of minutes, this correlation decreases, suggesting that the increase in performance seen during a single session is tied to the dissociation of the activity of direct and indirect neurons (right).

for basic scientific investigation of learning. Optical imaging has several advantages over electrode recordings, including providing a finer spatial resolution and allowing investigation of most neurons in a field of view. It can also provide a more unbiased view of the neural population, including neurons with low firing rates that may be missed using electrode recordings. Furthermore, optical recordings may facilitate the assessment of cell type and anatomical connectivity among the recorded neurons[13,14]. Conversely, it is easier to monitor deep brain structures with electrical recordings, as light scattering can limit recording resolution when attempting to penetrate far into neural tissue. Electrical recordings also provide finer temporal resolution than optical imaging, which is necessary if one seeks to study precise spike timing[3,15].

By working with mice, one can take advantage of the impressive array of genetic tools to selectively record from and manipulate the activity of subpopulations of neurons. This should allow for a careful dissection of the specific circuit mechanisms that underlie the learning of new behaviors. This new approach complements ongoing BCI work in nonhuman primates, for which most of these genetic tools are not now available. In nonhuman primates, however, it is easier to scale up the richness of the task from a one-dimensional auditory tone to a two-dimensional computer cursor or a multi-dimensional robotic arm. For basic science, this is important because richer BCI tasks are more likely than simpler BCI tasks to engage the complex, cognitive processes that underlie native arm control and other behaviors. Furthermore, for rehabilitation purposes, richer BCI tasks in nonhuman primates provide a more direct translation route to systems used with patients[5,6].

Whereas football fans can learn whether to flash up cards by determining where they are sitting in the stadium, the neural circuits and mechanisms that underlie the learning of new behaviors are still incompletely understood. The tool provided by Clancy *et al.*[1] enables a new view of the neural circuit, complementing existing tools for investigating the neural basis of learning. The field is now at a point where neuroscientists have a choice among powerful techniques for studying learning phenomena at multiple levels, from the subcellular through the neuronal to the circuit and systems levels. Go team!

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Impaired import: how huntingtin harms

Elizabeth A Jonas

We now learn that mutant huntingtin binds to a complex that imports constituent proteins across the mitochondrial inner membrane, halting bioenergetics in synaptic mitochondria and predisposing to neuronal dysfunction and death.

Mitochondria are the wellspring of life, increasingly heralded as necessary for the prevention of degeneration of vulnerable populations of neurons. Mitochondrial metabolism is crucial to neuronal function[1], and compromised mitochondria have been found in neurodegenerating cells[2], with mitochondrial dysfunction being implicated in every major neurodegenerative disorder, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease[3]. Whether mitochondrial dysfunction is the sole cause of the disorder or secondary to other deficits has continued to be debated, but understanding the implications of this question is important to determining the

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