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Systems Neuroscience: How the Cortex Contributes to Skilled Movements

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A recent study demonstrates how acute neural circuit manipulations can lead to overestimations of circuit function, while chronic manipulations can reveal compensatory modes of plasticity that restore behavior.

Understanding how specific neural circuits give rise to thoughts and actions remains a fascinating and fundamental question in neuroscience. A common approach in determining the role of a specific brain site in a given behavior is to inactivate that group of neurons, either transiently or permanently, and observe the effects on behavior. For these experiments, neurons can be shut down either permanently by creating a lesion, or temporarily by either pharmacological inactivation or, more recently, by using optogenetics. Optogenetics is an especially popular approach to altering circuit activity because it allows for neuronal activity to be manipulated with very high spatial and temporal precision, and it is easily reversible [1,2]. In that light, it is an appealing idea that optogenetics may provide a sleek new alternative to the use of lesions and other traditional methods. A new study from Bence Olveczky's group [3] cautions against that idea: these authors have shown that, much like the tale of the blind men touching different parts of an elephant, starkly different and potentially misleading conclusions can emerge from data collected using only one or the other approach. Their study highlights the value of integrating both classical and contemporary approaches to gain a more complete picture of the role that specific cortical neurons play in the performance of learned behaviors.

Adopting a comparative approach, Otchy *et al.* [3] focussed on two well-established model systems and their corresponding learned behaviors. Using rats, they investigated the role of the motor cortex in execution of a learned sequence of lever presses. And using songbirds, they investigated the role of the specialized sensorimotor cortical area, nucleus interfacialis (Nif), in performing the learned vocal sequence that defines adult song. In both systems, the authors found that transient inactivation of the targeted cortical area led to either a disruption or complete loss of the associated behavior. Taken alone, these results of transient inactivation suggest that the targeted structure is necessary for proper performance of the associated behavior. Permanent silencing of the same two regions, however, led to a gradual yet complete recovery of the two learned behaviors, even in the absence of additional instruction. In contrast to their initial observations, these results of permanent inactivation suggest that the lesioned cortical structures are *not* necessary for those behaviors (Figure 1).

Their integration of the two approaches gives a more complete view of the role of motor cortex in the performance of learned behaviors: intact versions of those structures are acutely required for expression of the behavior, but their presence is not required in order to achieve the full complexity of the motor sequence. The authors interpret those data as evidence that these cortical areas play a permissive role, rather than an instructive role, in the adult performance of these learned behaviors.

Otchy *et al.* [3] observed a recovery of learned behavior over the course of days following a sudden, but sustained, change in circuit function. What may be the mechanism underlying that recovery of behavior? The authors suggest that specific features of the behavior are encoded in the structure and function of downstream circuits, and that gradual recovery is most consistent with a type of homeostatic plasticity being activated in those downstream regions. They investigated that idea by modeling the function of vocal control circuits that lie downstream of Nif in songbirds. Building on previous ideas about the function of that microcircuit [4], Otchy *et al.* [3] modeled it as a kind of feedforward network known as a synfire chain that receives excitatory input from Nif. Acute removal of that excitatory input prevented many downstream neurons from reaching threshold, resulting in slowed or truncated versions of the simulated song behavior. They modeled homeostatic plasticity as either a reduction in threshold, an increase in input resistance, or an increase in the strength of remaining synaptic inputs. Each of those changes restored the song to its previous speed and decreased the expression of truncated behaviors.

Otchy *et al.* [3] are careful to note that the mechanisms that could underlie such a recovery will need to be further examined. Although their homeostatic model recapitulates their experimental findings, similar changes in circuit function can arise from different mechanisms [5]. For example, the gradual recovery of behavior could be due to recruitment of a parallel circuit. Much of what is understood about how a neuron or group of neurons can switch to a parallel circuit originates from studies in the crab stomatosensory ganglion (STG), which is composed of four different circuits that control the motor patterning of four regions of the foregut [6]. In the STG system, single neurons can switch between two different circuits, and, especially relevant to the findings of Otchy *et al.* [3], this switching is dependent on whether one or both networks are active [7]. The mechanisms underlying switching likely involve a redistribution of synaptic strengths or alterations in the intrinsic excitability of certain neurons that comprise the circuit [5]. Similarly, long-term visual deprivation ('dark-exposure') in adult mice has been found to trigger local circuit reconfiguration in layer 2/3 of the visual cortex, such that the relatively weak lateral inputs within this layer grow stronger, possibly allowing for the visually-deprived neurons to process other, non-visual information [8]. In the context of the songbird model, long-term silencing of Nif could induce the downstream circuitry (the HVC) to adopt or switch to a different parallel network, one that downplays the recently-lesioned input from Nif, and upregulates and strengthens the power of what was previously a less dominant circuit.

The Otchy *et al.* [3] study also prompts discussion about the function of Nif or the motor cortex in the corresponding learned behavior. Their data lend support to the emerging idea that motor cortex is essential for acquiring learned behaviors, but is not required for behavioral execution after learning is complete. For example, Olveczky and colleagues [9] also recently showed that mouse motor cortex is essential for acquiring skillful movements, but is not required for executing those learned behaviors. Those data suggest that a primary role of motor cortex in behavioral learning may be to 'tutor' subcortical motor circuits during skill acquisition. That idea is also supported by data on the role of Nif in songbirds. Nif conveys essential auditory information to downstream circuits as juvenile birds are engaged in memorization and imitation of a tutor song, but lesion studies reveal little or no impact of Nif on adult song performance [10,11].

The ability of Otchy *et al.* [3] to detect an acute impact of Nif inactivation on adult song performance is a tribute to their creative approach. They lesioned Nif and examined the properties of the associated songs, but there was no surgery or other disturbance between prelesion and postlesion recordings. The effect on song performance was most apparent immediately after lesioning Nif, and song gradually returned to its prelesion status within hours or days. This effect was not detectable by earlier researchers because the time course over which song recovers due to putative homeostatic changes is the same time course over which birds typically refrain from singing as they recover from surgery. By employing multiple approaches — both transient inactivation and traditional lesions — as methods of manipulating activity in their neuronal population of interest, Otchy *et al.* [3] demonstrate the depth of insight that can emerge from integrating classical, contemporary and comparative approaches to understand the neural basis of complex behaviors.

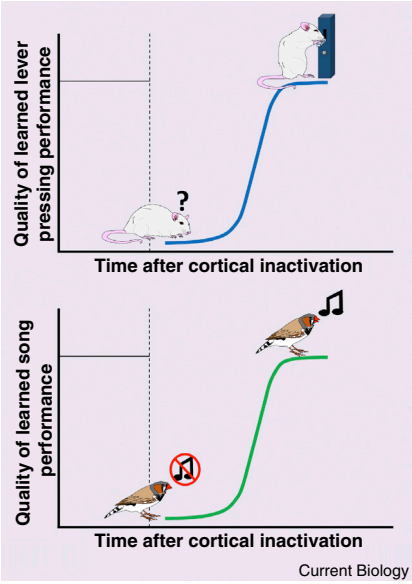

Figure 1. Transient silencing of a neural circuit can sometimes lead to an overestimation of its function. Permanent silencing can reveal compensatory mechanisms.
Top: in rats, acute silencing of the motor cortex abolishes a previously learned lever press task, but the behavior recovers if the same brain region is chronically silenced. Bottom: similarly, in songbirds, acute silencing of the sensorimotor cortical area Nif inhibits singing, but long-term silencing of the same region results in the recovery of the song. (Schematic by Harley Yerdon.)

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Evolution: Welcome to Symbiont Prison

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Can egalitarian partnerships exist in nature? A new study demonstrates how protist hosts use and abuse their algal symbionts depending on their needs. While this relationship allows protists to survive in low nutrient conditions, it leaves little room for algal retaliation.

From the deepest sea vents to the mountains with the highest elevation, symbionts allow their hosts to exploit new environments [1]. These partnerships between different species are remarkable not only in their ubiquity, but also in how partners evolve mechanisms to maximize their benefits in varying contexts [2]. Now a new study by Lowe *et al.* [3] in this issue of *Current Biology* adds to this marvel by demonstrating the precision by which hosts can gain benefits from symbionts across a gradient of environments — supporting them when needed and starving them when they are not.

Lowe *et al.* focus on the symbiosis between the protist host *Paramecium bursaria* and the algal symbiont *Chlorella* sp. (Figure 1A), which engage in a facultative photo-symbiosis found in shallow freshwater habitats [3]. In this partnership, endosymbionts provide hosts with maltose and oxygen derived from photosynthesis, and hosts provide endosymbionts with nitrogen compounds. Although identifying the products of symbiotic exchange has become easier with emerging techniques [4], quantifying the actual costs and benefits of symbiotic trade remains difficult. Lowe *et al.* are able to do this because the fitness of the two partners can be studied both engaged in symbiosis, or not.

The researchers independently manipulated light (affecting symbiont photosynthesis) and bacterial food (affecting host nutrients through heterotrophy), and then grew the partners either in a free-living state or in symbiosis. They found that while the growth rate of free-living hosts did not change with light levels, hosts with endosymbionts suffered net mortality in the dark and achieved the highest growth rates at highest irradiances. Calculating the net benefit of symbiosis across the manipulated environment, they found the highest payoff for hosts was at high light and low food availability — a potential driver for why hosts with endosymbionts are able to exploit nutrient-limited aquatic habitats [3].

So far, no surprises — this is the power of natural selection, organisms are selected to maximize the resources of their environment, whether it be by using their own mechanisms or exploiting the capacity of others [5,6]. Clearly the protist host has evolved ways to use the symbiont to its advantage under fluctuating nutrient and light environments. But do the symbionts show similar fitness-maximizing strategies? Lowe *et al.* found that while the free-living algal abundance increased at high light, the symbiotic *Chlorella* abundances decreased [3]. Why would a symbiotic, photosynthesizing *Chorella* experience a fitness cost of symbiosis at high light levels?

