Limber Neurons for a Nimble Mind

Earl K. Miller[1],* and Stefano Fusi[2]
[1]The Picower Institute for Learning & Memory and Department of Brain & Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[2]Center for Theoretical Neuroscience, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA
*Correspondence: ekmiller@mit.edu
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In this issue of *Neuron*, Stokes et al. (2013) demonstrate that cortical neurons that adapt their properties with task demands form patterns reflecting the shifting mental states needed to solve the task. Adaptive neurons may be critical to hallmarks of cognition: behavioral complexity and flexibility.

Traditionally, cortical neurons have been viewed as specialized for single functions or a few highly related functions. Different sets of neurons analyze space, recognize objects, etc. The thinking is that while a given neuron may participate in many behaviors, its activity always "means" one thing like "leftward motion." And, indeed, the cortex is organized by sensory and motor functions, has maps of external space, etc. But strict specialization may be the exception, not the rule, more evident in primary sensory and motor cortex or for exceptionally important information like faces (Gross et al., 1972; Kanwisher et al., 1997). Instead, at the higher levels of cortical processing, neural specialization waters down in a mix of disparate, seemingly unrelated, information. There is no obvious function that unites the variety of information signaled by individual neurons.

Consider recent examples from the lateral intraparietal area (LIP), a cortical area widely regarded as specialized for visuospatial functions. The same neurons showed independent selectivity for motion categories and unrelated information like shape categories (Fitzgerald et al., 2011; Rishel et al., 2013). Such multidimensional or mixed selectivity may apex in the prefrontal cortex (PFC), the "executive" cortex, where cognitively demanding tasks engage large fractions of neurons that encode different information in different tasks or different times in the same task (e.g., Cromer et al., 2010). Note that this does not mean that cortical areas are functionally equivalent. Certain information is emphasized, more explicit, or more orderly in some areas than others. But it is increasingly clear that the cortex is not a patchwork of high specialization.

Many areas may be special for certain functions but not specialized for them because cortical neurons are often a nexus of disparate information.

This mixed selectivity suggests "adaptive coding": neurons with extensive inputs from a wide range of external (sensory, motor) and internal (values, memories, etc.) sources (Duncan and Miller, 2002). There is no one message from such neurons. They can be recruited for different functions because their message changes with the activity of other neurons. This flexibility seems essential for complex behavior (more below). But thus far, much of the evidence has been indirect, based on mixed selectivity of single neurons and core brain areas in humans that are activated by many different cognitive tasks. In this issue of *Neuron*, Stokes et al. (2013) provide some of the first direct evidence for adaptive coding in action.

Monkeys were taught that six pictures formed three pairs. Then, they saw two randomly chosen pictures in sequence separated by a short delay. They were rewarded if they successfully indicated whether the two pictures were paired or not. Note the evolution and diversity of mental states: perception and short-term memory (for the first picture), recall (of its pair), and decisions (paired or not). Rather than use the typical approach of focusing on the average firing rate of single neurons over long intervals (seconds), Stokes et al. (2013) examined patterns of PFC neural activity recorded from multiple electrodes over small steps in time (50 ms). This revealed shifting patterns of PFC activity that followed a trajectory through multidimensional space from signaling sensory events to internal fac-

tors like rules and decisions. Many PFC neurons participated in multiple states. Thus, mixed selectivity does not result in cortical porridge but rather an organized progression of mental states, provided you have multiple electrodes and can simultaneously take multiple neurons into account.

Why such complexity? Would it not be simpler if every neuron had its own job? You could build a brain like that, but it would not work very well. Consider a simple neural circuit designed to solve the Stokes task (Figure 1). The readout neuron is active when the weighted sum of the inputs is above a threshold. As in the exclusive-or (XOR) problem, there is no solution if inputs include only specialized neurons that encode the pictures separately. Even in the simplest case of two pictures (A, B) and their pairs (A′, B′), the readout neuron cannot respond to the two related pairs (A, A′ and B, B′) and not to the other two (A, B′ and B, A′). The solution is to add neurons that respond to nonlinear mixtures of relevant variables. The task is solved by simply adding a third neuron that adapts its selectivity according to the cue stimulus (it discriminates A′ versus B′ only when the cue was A). In a forthcoming paper, we demonstrate that mixed selectivity in PFC neurons has critical computational advantages (Rigotti et al., 2013). It greatly increases the complexity and number of tasks that can be learned. Rather than "confuse" downstream readout neurons, increasing the number of mixed selectivity neurons exponentially increases the number of possible input-output mappings that readout neurons can implement. Networks without mixed selectivity have a limited capacity to learn
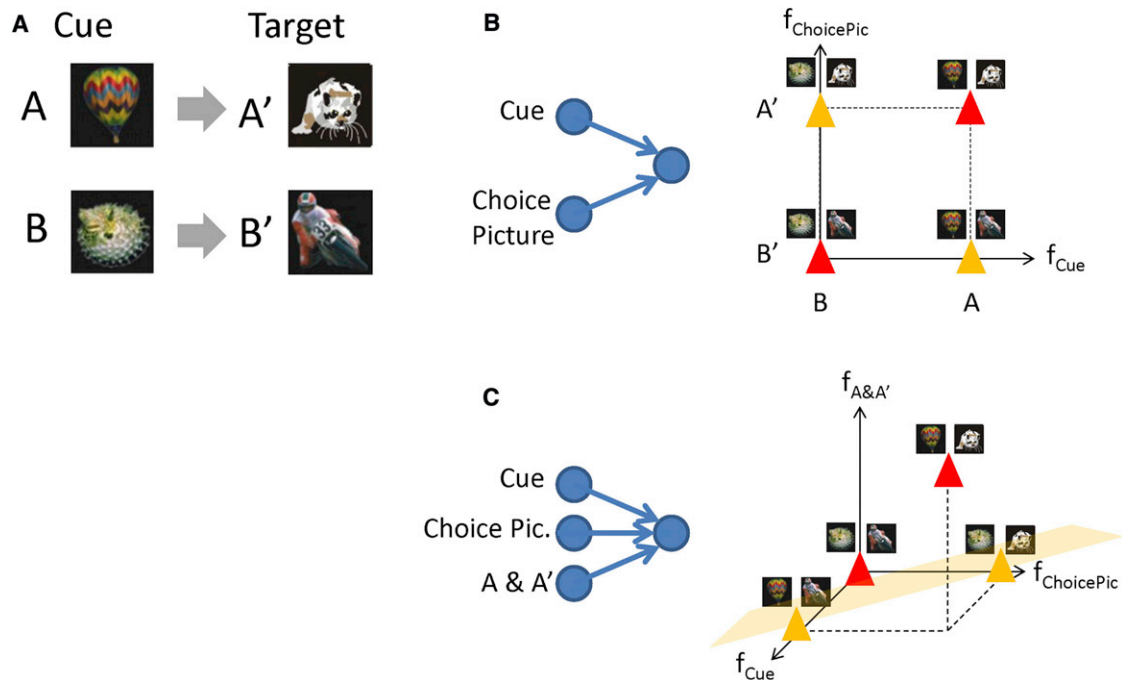
Figure 1. Example of a Neural Circuit that Can Solve a Task Only with Mixed Selectivity Neurons
(A) Cue and related target pictures. A is paired with A′, and B with B′.
(B) Left: two highly specialized input neurons converging on a readout neuron. One responds to A and not B and the other to A′ and not B′. Right: the x axis represents the activity level of one input neuron (A versus B) and the y axis the other (A′ versus B′). The four triangles are four possible input patterns for the cue and choices. Red triangles cannot be separated from yellow triangles with a line (the readout neuron cannot respond to A, A′ and B, B′ but not to A, B′ and B, A′).
(C) Same as (B) but a mixed selectivity neuron responding to the combination A and A′ is included. The input space is now three-dimensional, and red triangles can be separated from the yellow ones by a transparent plane.

a few simple tasks. Plus, mixed selectivity speeds and eases learning because only readout neurons need to be trained and, with high-dimensional neural representations, learning algorithms converge more rapidly (Rigotti et al., 2010). Given these advantages, it is no wonder that mixed selectivity is so widely observed in the cortex.

But does mixed selectivity not create problems? Do downstream neurons not sometimes receive signals that are irrelevant or counterproductive? One solution is the oscillatory brain rhythms. They could allow neurons to communicate different messages to different targets depending on what they are synchronized with (and how, e.g., phase and frequency). For example, rat hippocampal CA1 neurons preferentially synchronize to the entorhinal or CA3 neurons at different gamma frequencies and theta phases (Colgin et al., 2009). Different frequency synchronization between human cortical areas supports recollection of spatial versus temporal information

(Watrous et al., 2013). Different phases of cortical oscillations preferentially signal different pictures simultaneously held in short-term memory (Siegel et al., 2009). Monkey frontal and parietal cortices synchronize more strongly at lower versus higher frequency for top-down versus bottom-up attention, respectively (Buschman and Miller, 2007). Entraining the human frontal cortex at those frequencies produces the predicted top-down versus bottom-up effects on behavior (Chanes et al., 2013). Thus, activity from the same neurons has different functional outcomes depending on their rhythmic dynamics.

For years, experimentalists have observed that cortical areas central to cognition have large proportions of "weird" neurons with mixed selectivity that cannot be pinned to one particular message. These neurons may have seemed difficult to interpret, but there is mounting evidence that they may underlie hallmarks of cognition: the great capacity to absorb and flexibly implement a wide

range of cognitive skills and tasks. Stokes et al. (2013) provides a new intriguing glimpse into their neural infrastructure and dynamics.

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