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Neuron
Previews

The mode is the message

Matthew R. Krause[1] **and Christopher C. Pack**[1,*]
[1]Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada
*Correspondence: christopher.pack@mcgill.ca

http://dx.doi.org/10.1016/j.neuron.2023.05.030

In this issue of *Neuron*, Khazali et al.[1] record neural activity during coordinated reaches and saccades. They find that excitatory neurons link arm and eye movement regions of parietal cortex, creating a multiregional mode that predicts movement timing and direction.

One of the most famous products of neuroscience research is the motor homunculus, created by Wilder Penfield to illustrate how much brain tissue is devoted to controlling each part of the body. This "grotesque creature" is immediately captivating because of the disproportionate size of its mouth and hands. However, it also conveys an even more important principle of cortical organization, namely the localization of function: each body part is neatly assigned to one part of the motor cortex. The idea of localization of function has animated neuroscience research from its beginnings,[2] and today a dizzying array of sulci, gyri, nuclei, and fields have been ascribed specific and localized functions.

That said, it is easy to attribute too much significance to the idea of localization. In fact, the picture generated by the homunculus is somewhat misleading, as electrical stimulation of the motor cortex can often elicit complex movements of multiple effectors.[3] This is arguably the natural state of the brain because, outside of a laboratory environment, movements seldom involve only a single limb. How does the brain coordinate movements that involve more than one effector?

This has been a controversial question. One line of reasoning argues for simplicity. Perhaps the effectors are not very well coordinated at all, and the apparent coordination arises because each one makes very accurate movements on its own. In other words, the fact that we can move both arms to pick up a heavy object simply reflects the precision of motor cortex commands in each hemisphere. Such an approach resembles one an engineer might use to build a system with standardized off-the-shelf parts and a single central controller. In the limit, this entails a role for the human motor system similar to that of the octopus, with each effector acting according to its own instructions and goals. While this is perhaps an unrealistic picture of the primate nervous system, proposals for largely independent effector control have been influential in motor control research, notably in studies of eye-head gaze shifts[4] and eye-hand coordination.[5]

An alternative framework is one in which brain regions that control different effectors interact extensively during the execution of complex movements. In this case, one would expect to find evidence for an exchange of signals between brain regions ostensibly devoted to the control of specific effectors, and, indeed, prior work in the gaze control system shows exactly that.[6] However, it has been challenging from a methodological perspective to identify the biological properties of these signals. That is the topic of the paper by Khazali et al. in this issue of *Neuron*.[1]

The authors made use of coordinated eye-hand movements, in which non-human primates executed an eye movement and a reaching movement toward the same target. Because eye movements and hand movements are generated by distinct pools of motor neurons, the combined movement must be generated centrally, most likely in the cerebral cortex. Indeed, previous work would suggest that the coordination probably occurs within the parietal lobe of the cortex, as patients with parietal lesions often demonstrate a fascinating deficit called magnetic misreaching, in which they are unable to dissociate the direction of reaching from the direction of gaze.[7]

More importantly for the current work, one part of the parietal lobe, the intraparietal sulcus, seemingly contains distinct representations of eye and hand movements, localized on its lateral and medial banks. This anatomical specialization provides an ideal way of looking for neural traces of coordinated movements: such coordination should manifest as an exchange of information between the two banks of the sulcus during combined eye and hand movements, but not during separate movements of the eye or hand.

Even with this dramatically narrowed focus, the problem of detecting traces of cross-area communication is still rather daunting. Each area contains millions of neurons that could communicate in complex ways, through direct or indirect, inhibitory or excitatory connections. Such complex wiring will necessarily lead to a buzz of activity in both areas, whether coordinated communication is happening or not. The challenging analytical question is how to detect the relevant signals from the background hum of the brain?

Much previous work has examined long-range communication in the brain, often by relying on temporally synchronized activity between local field potentials (LFPs), signals that capture the combined electrical activity of many cells near the tip of recording electrodes. There is evidence that synchronization between LFPs is indicative of information being exchanged between areas between populations of cells.[8] The paper by Khazali et al. goes a step further by using dual coherence, an extension of LFP-LFP coherence that requires a single neuron in one area to synchronize the firing of its spikes to LFPs in two areas, one of which is remote from the site of the neuron. This is important, because spikes are the currency of communication in the nervous system, and so a neuron whose spikes are synchronized to both local and distant sources is probably involved in communication between them.

Khazali et al. show, first using computational modeling, that dual coherence can separate localized neuronal clusters that control individual effectors from distributed circuits that coordinate multi-effector behavior. The latter is called the multiregional mode. Next, Khazali et al. show that this multiregional mode emerges clearly in neurophysiological data recorded from the eye and reach regions of the primate parietal cortex. Moreover, its activity predicts trial-to-trial variation in the properties of the eye-hand reaches, such as their latency and direction. Critically, this correlation only exists in trials where the animal is making a combined eye and hand movement, not when only one effector is used.

Finally, and perhaps most interestingly, the authors were able to estimate the neuronal cell types that are responsible for carrying the relevant signals. They did this by assigning each of their neurons into various types of excitatory and inhibitory categories, based on analysis of the corresponding spike waveforms. The results indicated that the multiregional mode is largely the product of interactions between excitatory neurons in each area, with inhibitory neurons shaping activity within local neuronal clusters. Thus, Khazali et al. were able to isolate a signature of intracortical communication that is responsible for coordinated movements and to identify a putative cellular basis for it.

The idea that neural circuits can rapidly organize themselves into ‘‘assemblies’’ that support complex behavior is an old one, but it has been difficult to characterize these circuits experimentally. Existing functional methods, such as brain imaging, often sacrifice spatial resolution, while anatomical measurements cannot reveal how the importance of different connections changes dynamically with behavior. The multiregional mode estimated by Khazali et al. therefore provides a glimpse of widespread functional interactions while retaining the necessary resolution to examine the properties of individual neurons.

This kind of analysis could ultimately be useful for reading or controlling brain signals. For brain-machine interfaces, the multiregional mode could provide a way of picking out those signals that carry information about intended movements from among the many possibilities available in multi-channel recordings. Moreover, previous work from the same lab has shown that brain stimulation can be used to manipulate the multiregional mode. Although that work relied on invasive stimulation, other studies have shown that non-invasive stimulation can affect multiregional communication as well. Specifically, Krause et al. showed that the entrainment of spikes to LFPs in remote areas predicts the speed of learning and that this entrainment can be modulated in a simple and effective non-invasive way.[9] Thus, future work could be aimed at detecting, decoding, and manipulating multiregional communication rather than focusing on individual groups of neurons.

This work more generally highlights the ways in which sophisticated methods can be used to extract meaning from complex anatomy and physiological signals. This is important because complicated circuits are a hallmark of brains throughout the animal kingdom. Recent work shows that, contrary to popular belief, even octopuses have eye-arm coordination,[10] so neuroscientists who are interested in motor control would do well to consider the possibility that the multiregional mode is the message.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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