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NEUROSCIENCE

The ripple effect of a single neuron

The contribution of a single neuron to brain function might seem negligible. But a map of the influence of single neurons reveals a complex pattern that prevents redundancy and enables clear messaging. SEE ARTICLE P.334

IKUKO T. SMITH

When a drop hits a pool of liquid, concentric cascading ripples form. Studying these ripples gives us information about the properties of the liquid and its molecules, such as their identity, mass, density or velocity. On page 334, Chettih and Harvey[1] take a similar approach to unravel the functional properties of the neural circuitry of the primary visual cortex in mouse brains: they trigger a small increase in the activity of a single neuron that causes a ripple of network activity in a pool of neurons.

The authors used a method that they call influence mapping to directly measure the effect of individual neurons on the activity of neighbouring ones. They genetically modified mice so that light-sensitive ion channels were expressed in neurons, and then used light to control neural activity (an approach called optogenetics). The mice were also made to express a fluorescent indicator of calcium concentration, which works as a reporter of the neurons' electrical activity (a technique called calcium imaging). Optogenetic stimulation triggered several spikes of activity (action potentials) in target neurons. Chettih and Harvey then used calcium imaging to measure the influence of a single manipulated neuron on the spiking activity of neighbouring neurons.

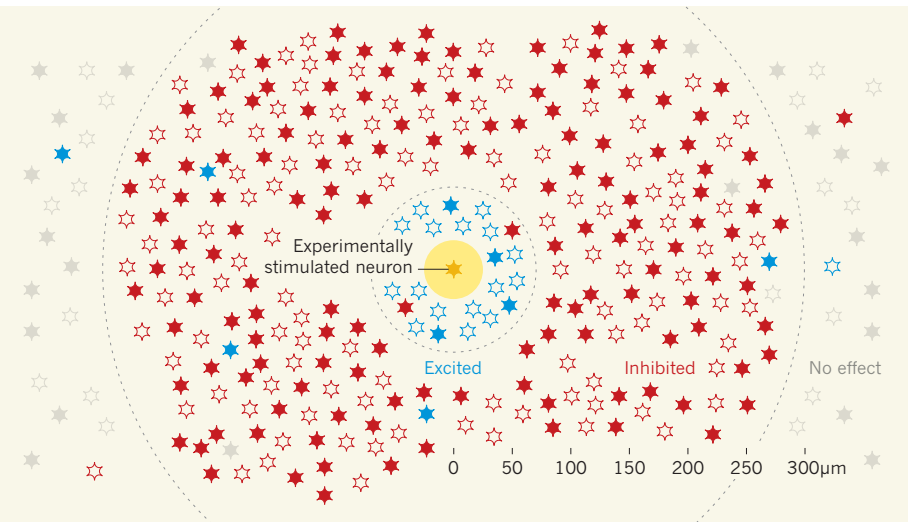

Figure 1 | Influence of a single neuron on the surrounding network. Chettih and Harvey[1] describe a model of network computation in the mouse visual cortex. They found that experimental stimulation of a single neuron (yellow) predominantly caused widespread inhibition (red) of the activity of neighbouring neurons. Stimulation also had an excitatory effect (blue) at short distances (25–70 μm), which affected a small proportion of neighbouring neurons, and almost no effect (grey) on neurons at long distances (more than 300 μm). Full stars represent neurons tuned to respond to similar features of the visual stimuli to the target neuron, and outlined stars represent neurons tuned differently. Within the area of predominant inhibition of neural activity (70–300 μm), neurons similarly tuned to the target neuron were more strongly inhibited than were differently tuned ones. This general like-to-like suppression regime (called feature competition) was peppered with sparsely distributed nodes of activating influence involving a small number of neurons whose visual responses were highly similar to that of the target neuron (feature amplification). Together, these two modes of information processing minimize redundancy and promote accurate coding of visual stimuli.

A few extra action potentials in a single neuron are but a drop in the bucket for a complex, intertwining network of neurons. But when the authors considered the distance between the target and neighbouring neurons, as well as their functional characteristics (that is, whether they respond in similar or different ways to visual stimuli), a meaningful picture emerged. Their model of functional connectivity gives us a glimpse of the fundamental computation performed in the primary visual cortex.

In the past 15 years, studies of single neurons in live animals have improved our knowledge of how individual neurons are connected in, and contribute to the overall function of, their network[2–7]. Many of these studies have focused on the neural circuitry of the cortex, in which the connections between neurons, called synapses, are abundant but generally weak[5]. These properties of cortical synapses suggest a type of network computation in which the spiking activity of a single neuron would mean very little. Yet experimental evidence has shown that stimulation of a single neuron can have behavioural consequences.

For example, electrical stimulation of a single neuron in the motor cortex can cause whisker movements in mice[6]. In rats, a similar stimulation of individual neurons in the barrel cortex, which is involved in processing sensory information, can trigger a licking behaviour associated with touch perception[7]. Curiously, cortical networks seem to be sensitive to the activation of some, but not all, stimulated neurons[6,7]. Chettih and Harvey provide an explanation for this observation.

The influence-mapping approach makes it possible to analyse a larger population of neurons than those studied using electrophysiology[4,8]. More importantly, it enabled the authors to categorize neuronal influences according to the degree of similarity between the responses of the manipulated neuron and those of the neurons it affects[2,3]. Notably, the subtle stimulation of neurons achieved with optogenetics is unlikely to elicit a strong generalized response and change the brain's state[9]. This approach might more closely mirror the basic computation of the cortical circuitry than other approaches.

Chettih and Harvey predominantly observed widespread suppression of neural activity around the target neuron (Fig. 1).

They also saw that the influence of a neuron on the surrounding network changed with distance: it exerted an excitatory influence on a small population of neurons at short distance (25–70 micrometres); an inhibitory influence at medium distance (70–300 μm, with maximum suppression at about 110 μm), affecting most of the neighbouring neurons; and had little influence at long distance (greater than 300 μm).

The authors' subsequent in-depth analysis revealed a much more complex pattern than a general inhibition of neural activity. They found that the extent of the influence of neurons on other neurons was related to how they responded to certain features of visual stimuli, such as orientation and temporal frequency. When a neuron was activated, neurons that were tuned to respond to similar features to that neuron were more strongly suppressed than were neurons with a different tuning. This inverse relationship remained true regardless of the distance between neurons. However, scattered within the ripples of influence, the authors also found a sparsely distributed group of neurons that were similarly tuned to the target neuron and strongly excited by it (Fig. 1). The response patterns of these neurons were also well correlated in time with that of the target neuron (that is, their moment-to-moment electrical activities closely resembled each other).

The authors' findings suggest that the complex network of the central nervous system works by balancing two parallel modes of computation. A predominant inhibitory influence between neurons that have similar tuning (which the authors call feature competition) is peppered with sparsely distributed pockets of excitatory influence among well-correlated neurons (which they call feature amplification). The model beautifully illustrates how feature competition reduces redundancy and enables inputs that are meaningful signals to be separated from those that are muddling noise, whereas feature amplification further improves the ability of select neurons to effectively carry information about the stimulus.

The work by Chettih and Harvey raises several questions. What are the cellular underpinnings of the widespread neuronal suppression that promotes feature competition? Inhibitory interneurons act locally to suppress other neurons' activity, and distinct types of interneuron have different responses to stimulation. For example, a burst of more than five action potentials in a neuron can induce a spiking response in approximately 30% of the neighbouring somatostatin-expressing (SOM^+) interneurons, whereas parvalbumin-expressing (PV^+) interneurons do not seem to respond to such stimulation[3] (although contrasting findings have been reported[4]). Chettih and Harvey added, on average, six action potentials to target neurons using optogenetics. This profile of stimulation might make the activation of SOM^+ interneurons more likely than that of PV^+ interneurons. Notably, the SOM^+ interneurons are more selectively tuned than PV^+ interneurons[10]. A preferential recruitment of the tuned inhibitory neurons could potentially bias the network response towards feature competition.

Finally, how is the encoding of stimuli by the brain affected by the animal's behavioural state? Does the cortical network use different coding schemes for different behavioural or environmental contexts, in a way that affects the pattern of the neuronal responses[9]? Would the 'ripples' in a neural network change dramatically under a greater impact, much like the behaviour of a non-Newtonian fluid, like ketchup? That remains to be seen. ■

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IMMUNOLOGY

Inflammation clues in STING protein structure

The STING protein aids intracellular defences by triggering inflammation. Studies that uncover how STING is activated might lead to strategies for targeting this protein in the treatment of cancer or autoimmune diseases. SEE LETTERS P.389 & P.394

ANDREA ABLASSER

The branch of the immune system called innate immunity has a pivotal role in host defence by recognizing general hallmarks of disease-causing agents. The intracellular protein STING, a transmembrane protein usually located on an organelle called the endoplasmic reticulum, is a key regulator of this type of immune response[1]. Writing in *Nature*, Shang *et al.*[2] (page 389) and Zhang *et al.*[3] (page 394) report full-length structures of STING, including STING in complex with the kinase protein TBK1, which initiates the downstream signalling pathway that is triggered on STING activation.

The abnormal presence of double-stranded DNA in the cytoplasm is a potent danger signal that activates STING. If the enzyme cGAS senses such DNA[4,5], it makes the molecule cGAMP; when this binds and activates STING, a signalling cascade begins that eventually alters gene expression to generate proinflammatory molecules. Abnormalities in this defence mechanism can underpin a spectrum of conditions, including cancer, autoinflammatory syndromes or neurodegenerative diseases[6–9]. STING is thus a highly promising drug target[10], but for such efforts to succeed, it is essential to understand how STING activity is regulated.

Previous studies[11–13] have illuminated how the cytoplasmic domains of STING interact with cGAMP and how the downstream signalling events that follow STING activation are triggered. For example, cGAMP binds to a V-shaped pocket that is formed by the cytoplasmic domains of two STING proteins that make a dimer[11] and, after undergoing a conformational change, STING is transported to an organelle called the Golgi complex, where it recruits TBK1 (ref. 12). Despite such progress, how cGAMP binding causes STING activation and facilitates the subsequent downstream signalling events was unknown.

Shang and colleagues used the technique of cryo-electron microscopy (cryo-EM) to generate near atomic-resolution structures of full-length human STING without cGAMP bound to it, and full-length chicken STING with and without cGAMP bound. Without cGAMP bound, the STING dimer is stabilized by interactions between different domains in each STING protein and between domains of the two different STING proteins.

A transmembrane helix is linked to the cGAMP-binding domain through a connector element — made up of a connector helix and a connector loop — that forms a crossover point between the two STING proteins. In the cGAMP-bound state, the connector elements and the cGAMP-binding region of each subunit unwind, causing a 180° rotation