NEUROSCIENCE

Neural Networks Debunk Phrenology

Intracortical recordings reveal that distinct regions of the mammalian brain must synchronize their activity to support certain behaviors.
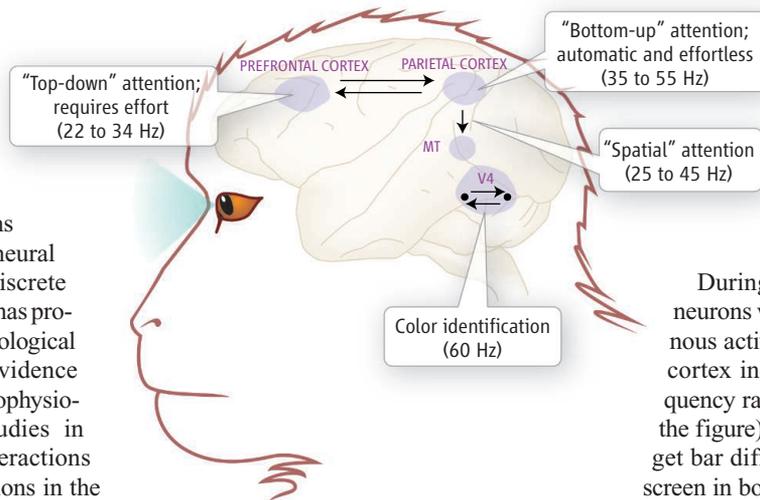
Robert T. Knight

Systems neuroscience aims to understand how billions of neurons in the mammalian brain support goal-directed behavior, such as decision making. Deciphering how individual neurons respond to sensory inputs or motor decisions has focused on delineating the neural basis of these processes in discrete regions of the brain's cortex, and has provided key insights into the physiological basis of behavior. However, evidence from neuropsychological, electrophysiological, and neuroimaging studies in humans has revealed that interactions between widespread neural regions in the brain underlie fluid, organized behavior. Two papers in this issue, by Womelsdorf *et al*. on page 1609 (*1*) and Saalmann *et al*. on page 1612 (*2*), and a recent paper in *Science* by Buschman and Miller (*3*), unravel the details of these interactions by assessing the simultaneous activity of neurons in multiple sites of the mammalian brain. The studies show that network interactions among anatomically discrete brain regions underlie cognitive processing and dispel any phrenological notion that a given innate mental faculty is based solely in just one part of the brain.

Buschman and Miller used a classic experimental approach of manipulating "top-down" and "bottom-up" attention in monkeys. Top-down searching—for example, searching for the infamous Waldo character in a children's book illustration—typically requires effort. By contrast, bottom-up searching is predominantly an automatic behavior, such as finding a red balloon in a sea of blue balloons—the red balloon literally "pops out" of the visual scene. Buschman and Miller recorded neuronal activity from multiple sites in the prefrontal and parietal cortical areas of the monkey brain (the cortex is largely responsible for high-level cognitive processes such as attention, memory, and decision-making).

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"Top-down" attention; requires effort (22 to 34 Hz)

PREFRONTAL CORTEX PARIETAL CORTEX

MT

V4

"Bottom-up" attention; automatic and effortless (35 to 55 Hz)

"Spatial" attention (25 to 45 Hz)

Color identification (60 Hz)

Communicating at a distance. Oscillatory neuronal (electrical) activity in defined frequency ranges supports synchronous interactions between anatomically distinct regions of the mammalian brain (illustration of rhesus macaque shown) during cognitive tasks that require deliberate or automatic attention, memory, or visual processing.

These regions are several centimeters apart, but are connected by extensive bundles of axons (neuronal extensions that form the circuitry of the brain), suggesting that they might communicate with each other while the animal performs behavioral tasks. In classic single-neuron recording studies, different brain areas are examined by different investigators, who observe different tasks in different animals. The advantage of recording from multiple sites in the brain simultaneously is that these factors are held constant, thus allowing precise analysis of the relative timing of neural activity in the same animal.

Buschman and Miller determined both the electrical activity of individual neurons (called single-unit activity) and the net ensemble activity of many neurons (called the local field potential) in the monkey brain. Repetitive activity of these neuronal ensembles is manifested as oscillatory activity in different frequency bands, which can be readily extracted from the ongoing electrical activity of the brain. During a top-down serial visual search, the monkeys had to detect a colored bar (the target) that shared color and line-orientation properties with other bars on a computer screen. Because the target bar was similar to other bars on the screen, the monkey had to search to pick out the salient target, a task requiring deliberate effort.

During this task, prefrontal cortical neurons were activated first, and synchronous activity with neurons in the parietal cortex increased in the 22 to 34 Hz frequency range in the prefrontal cortex (see the figure). For the bottom-up task, the target bar differed from all other bars on the screen in both color and orientation, leading to rapid and effortless identification. In response to this scheme, parietal neurons were activated first, and synchronized activity with the prefrontal cortex was observed at a frequency range of 35 to 55 Hz in the parietal cortex. The findings highlight two-way interaction between these distinct regions of the mammalian cortex, with communication pathways tuned to different frequencies.

The work by Saalmann and colleagues extends these observations, using single-unit and local field potential recordings focused on the effect of the parietal cortex on the area that perceives motion (MT area) of the monkey brain. The MT is connected to many different cortical regions of the brain and plays a major role in perceiving movement. Because the posterior parietal cortex is involved in spatial processing, Saalmann *et al.* reasoned that it might communicate with the MT. For these experiments, a monkey has to judge whether two sets of stacked bars, presented half a second apart from each other, match in both the spatial location of the bars and their orientation in space. As in the Buschman and Miller study, neuronal activity was recorded simultaneously in the parietal and MT sites of the brain. The authors detected single-unit activity in the posterior parietal cortex before that in the MT, and synchrony between these two regions at a 25 to 45 Hz frequency range in the MT. A phase delay in synchronous activity between these two regions is indicative of a top-down effect of the posterior parietal

cortex on the MT during this matching task.

Using a similar experimental logic, Womelsdorf *et al.* analyzed three single-unit activity and local field potential data sets obtained from cats and monkeys. These activities were recorded from areas in the brain (called 18 and 21a in the cat and V1 and V4 in the monkey) involved in vision, including color, object, and stereoscopic processing. The authors observed that the phase delay (in milliseconds) of oscillations in the local field potential between nearby sites (from 1 mm to 1 cm apart) determined the efficacy of synchronized neuronal activity between the sites. It has been shown previously in animals that local field potential in the frequency range of 4 to 7 Hz predicts both single-unit activity and higher frequency (30 to 200 Hz range) oscillatory activity (*4*). This local mechanism, involving coupling of a brain rhythm and single-unit activity, has been proposed to synchronize neural activity between regions, enabling effective communication between brain areas (*5*).

Taken together, the three papers indicate that top-down signals between brain regions regulate the flow of information and that distributed neural networks that use oscillatory dynamics support a broad spectrum of neural processing and behavior. The results in cats and monkeys also nicely parallel findings in humans. For instance, brain lesion, electrophysiological, and neuroimaging research in humans (*6*, *7*) has shown that top-down signals from prefrontal and parietal cortices regulate attention and working-memory capacity. The findings in animals that oscillatory dynamics support network activity and enhance the efficacy of synchronized activity between distributed neural regions has also been observed in humans. Intracranial data from subdural electrodes in the human cortex have shown that oscillations in the 4 to 7 Hz frequency range are coupled to high-frequency oscillations in the 30 to 150 Hz range in areas similar to those studied in the monkey brain by Buschman and Miller and by Saalmann *et al.* Further, this particular coupling mechanism is used to delineate task-specific network activity (*8*, *9*). A recent human intracranial study reports that single-unit activity in the human brain is synchronized to local field potentials in the 4 to 7 Hz and 1 to 3 Hz frequency ranges in the hippocampus (*10*), further supporting the observations initially reported in animals.

It is now widely agreed that defining network interactions is key to understanding normal cognition. There are also numerous psychiatric disorders, such as depression, seasonal affective disorder, mania, and even some cases of psychosis, that are episodic and are not associated with defined neuroanatomical damage. Might it be that some of the periodic symptoms are caused by intermittent network dysfunction, caused by disturbed oscillatory dynamics? If so, then the work by Buschman and Miller, Womelsdorf *et al.*, and Saalmann *et al.* may have a great impact on our understanding of these disorders.

One mystery remains: How is information in oscillatory activity encoded? The individual spike train rate (the number of times a neuron fires each second) or spiking frequency (the rhythm at which a neuron fires) is not sufficient for coding the vast array of processes that underlie perception, memory, or decision making. Nevertheless, the three groups have laid the groundwork for deciphering this neural code.

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MATERIALS SCIENCE

Food Pathogen Detection

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New methods for detecting food pathogens can quickly identify single microbes, but major hurdles must be overcome before they can be introduced to practical use.

The detection of food pathogens is crucial for food safety; detection methods must be fast, sensitive, and accurate. Yet, almost all techniques used today to identify specific pathogens in foods take at least 48 hours, and some take as long as a week. Further confounding the challenge is the need to address "zero tolerance," a standard that mandates that no viable pathogens are allowed in certain foods. To meet zero-tolerance levels, detection methods need to be sensitive down to a single pathogen in a prescribed sample. Current methods require several days to achieve this standard, because they rely on culturing the pathogen to increase its numbers to detectable levels.

In contrast, modern detection systems currently under development analyze food based on the detection of a specific spectroscopic, immunological, or genetic signature (see the figure). These methods are potentially faster than currently used methods by virtue of their enhanced sensitivity, with a detection limit of a single cell, in some cases in real time. However, the methods have not yet been introduced to practical use, because they are difficult to integrate with sample preparation and handling practices (*1*). Sample preparation is tedious because the target pathogens cannot be extracted and concentrated by simple physical means. In addition, sample preparation typically depends on the nature of the sample. Thus, extracting pathogens from water is different than extracting the same pathogens from milk, let alone ground beef.

Furthermore, it is often difficult to assess the efficacy of the new methods as compared to the classic means of detection, because the former are rarely tested on real food samples and do not necessarily yield results that can be translated into commonly accepted units of measure (such as colony-forming units). Finally, methods that are rapid and sensitive must also to be field-portable. A method that requires the sample to be shipped to a central laboratory for analysis with sophisticated equipment introduces a delay in the overall time to complete the analysis.

Not even the question "what do we want to know?" has a simple answer. The symptoms induced by a food pathogen are obvious, especially to the victim, but biochemical and metabolic differences between virulent and nonvirulent strains may not be as dramatic. The genome of *Escherichia coli* O157:H7 differs vastly from that of its cousin *E. coli* K-12 (*2*), but from a biochemical perspective, they are very similar. The fundamental question is thus whether a food contains a pathogen that causes a person to become ill

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