oxygen. There, oxygen molecules, protons, and electrons must all meet and interact at what is called a "three-phase boundary" (see the figure). Physically, this boundary is defined by the intersection of the platinum catalyst, the empty pore space for gas diffusion, and the proton-conducting-polymer, or "ionomer," of the membrane. If the pores are too small, then no oxygen can pass through. Under perfect conditions, the oxygen and protons would combine with electrons to form water at this boundary ($O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$ + energy). Unfortunately, the ionomer can coat the platinum catalyst and block access of oxygen to the catalyst site during the manufacturing process.

Prior work has studied porous frameworks to improve gas diffusion at the three-phase boundary but faced challenges with chemical stability or small pore size (*2*–*4*). For example, metal-organic frameworks (MOFs), which consist of organic ligands and metal ions that organize into porous crystal lattices, have relatively small pores (<2 nm) that yield a relatively larger gas diffusion resistance. By contrast, covalent organic frameworks (COFs) have larger pores that allow for faster transport of oxygen to the catalyst (*5*, *6*). However, both MOFs and COFs face stability issues involving hydrolysis and temperature. MOFs, in particular, are susceptible to dissolution in water, as a by-product of the fuel cell reaction. By contrast, COFs can undergo thermally activated reversible reactions that cause dissolution. To overcome the stability issues and maintain proton conduction pathways and porous networks, several studies have examined COFs with more stable chemistries (*7*–*10*). These COFs incorporate polar or sulfonate groups to guide proton conduction through the pores.

Although each of these studies made singular advances, it is challenging to find a COF or MOF that addresses the multitude of challenges faced in the proton exchange membrane fuel cell environment. In the context of this prior work, Zhang *et al.* address the issues of porosity, stability, and performance all together in a single COF material. They improve the structure of the three-phase boundary by enhancing the accessibility for oxygen to reach the catalyst. They designed a COF with mesopores (2.8 to 4.1 nm) lined with sulfonate groups for use in conjunction with the ionomer in the electrode assembly. COFs contain organic building blocks that arrange into two- and three-dimensional porous crystalline lattices. These pores are just wide enough to allow oxygen molecules to reach the catalyst, and the sulfonate groups provide sites for proton transport. By exploring several COFs, the effect of pore size is revealed.

As a result of this improvement, the platinum utilization and the peak power increases by 60% relative to electrodes without the COF. Further, the sulfonate groups on the COF displace parts of the ionomer that would otherwise cover up the platinum catalysts, opening more surface area for oxygen to access by going through the pores in the COF.

This work bears some resemblance to a previous work that demonstrated advantageous proton conduction across porous channels in COFs, in which the larger pore size was advantageous (*11*). Recent work has shown that the void space could be better utilized by increasing ion exchange capacity through the introduction of multiple proton-conducting groups into the framework (*12*). These strategies could help future design in the pursuit of even more effective ion-conducting COFs for proton exchange membrane fuel cells. Zhang *et al.* address the multiple challenges faced by the oxygen reaction at the fuel cell electrode, which is currently a major limiting factor. The designed COF is porous enough to allow for oxygen diffusion, conductive toward protons, and stable in the extreme environment of the electrode. As a result, the electrode's platinum catalyst is more effectively utilized. The broader impact is that COFs such as these could lower the long-term price of fuel cells by minimizing the platinum required and improving the practicality and competitiveness of the hydrogen fuel cell. ■

"...covalent organic frameworks... could lower the long-term price of fuel cells..."

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NEUROSCIENCE

Creating a window into the mind

A noninvasive imaging technique measures neuronal activity at a millisecond time scale

By **Timo van Kerkoerle[1]** *and* **Martijn A. Cloos[2]**

How does the brain generate the mind? For example, it remains a mystery how the neurons in our brain allow us to see these letters, understand this sentence, and decide whether to stop reading or continue. Finding answers to these questions could give an objective understanding of "self," as well as help clarify the mental disorders that affect large numbers of people, such as depression, schizophrenia, and autism. On page 160 of this issue, Toi *et al.* (*1*) describe a promising new magnetic resonance imaging (MRI) method that could measure the activity of neurons at time scales relevant to mental processes.

The development of functional MRI (fMRI) in the 1990s was revolutionary (*2*), offering a way to view activity patterns in the human brain noninvasively. This has made it possible to map regions in the brain that are involved in cognitive functions such as perception, understanding, and decision-making. However, fMRI is limited in its ability to pinpoint the time and place of neuronal activation (the temporal and spatial specificity). fMRI measures changes in the blood oxygenation level–dependent (BOLD) signal (*3*), which is a surrogate for neuronal activity (*4*). BOLD reflects the hemodynamic response of the brain, which comprises changes in blood circulation that are evoked by changes in neuronal activity. When viewed through this "hemodynamic lens," the inferred activation is blurred in space and time.

Spatial blurring in fMRI relates to the vascular architecture. Large veins near the surface of the brain, which drain large cortical areas, have great sensitivity but limited speci-

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ficity (*5*). One way to improve the specificity of fMRI is to focus on smaller veins by using stronger magnetic fields (*6*). This has led to a surge of "ultra-high-field" fMRI systems that allow an increase in resolution (see the photo). Fundamentally, the spatial specificity of BOLD is limited because the vessels form large networks where an increase in the size of vessels at one location will also cause changes in downstream vessels. So even the smallest vessels can change their size in response to the activity of faraway neurons (*7*). The spatial specificity of optical imaging of blood vessels is superior to that of fMRI (*8*), which suggests that fMRI systems with increased magnetic-field strength have much to offer.

The temporal specificity of fMRI is perhaps a more pressing limitation. Although hemodynamic fluctuations can be surprisingly fast (~1 s) (*9*), this is still too slow to follow neuron activation during cognitive processes such as perception and decision-making (~0.1 s) (*10*). The difficulties result from a delay in the hemodynamic response, which also remains increased for some time after neuronal activity has returned to baseline. Effectively, the hemodynamic response imposes a filter that suppresses the detection of rapid changes along the temporal dimension. This limited temporal specificity is also observed with optical imaging techniques (*11*).

The results of Toi *et al*. suggest that their method, called DIANA (direct imaging of neuronal activity), provides a signal that reflects the intracellular voltage of a population of neurons, avoiding indirect physiological limitations on the temporal and spatial specificity that can be reached. Furthermore, DIANA does not require contrast agents or new equipment; all that is needed is a simple modification to the control software used to operate existing ultra-high-field MRI systems. The exact biophysical underpinning of DIANA is not completely clear. The leading theory suggests that changes in neuronal membrane potential are reflected in the transverse relaxation time (T_2) of the MRI signal. Simply put, T_2 determines how quickly the MRI signal disappears. Initial estimates suggest that a ~0.1% signal increase can be observed during neuronal activity, which is caused by a membrane potential–induced lengthening of T_2. Although further study is needed to develop a better understanding of the DIANA contrast mechanism, the high spatial and temporal specificity of the activity patterns reported by Toi *et al*. could open a new window into the brain.

The 11.7-tesla magnetic resonance imaging (MRI) scanner at NeuroSpin in France (shown here) has, at present, the highest magnetic-field strength among MRI systems designed for human brain imaging.

fMRI studies have found that cognitive functions generally require networks of brain areas, but it has been challenging to disentangle the precise role of the different nodes in these networks (*12*). Notably, the temporal precision of DIANA could allow measurement of the small delays in the activation patterns across nodes, revealing how messages are relayed in networks (*13*). Toi *et al*. show that they can observe temporal delays between cortical layers in mouse brain (on the order of tens of milliseconds), which could even help to disentangle processing streams within an area (*14*). Furthermore, an exciting advantage of measuring intracellular voltage is that it enables distinction between excitatory and inhibitory signaling between neurons, something that is generally not even possible with highly invasive methods, such as electrodes implanted in the brain (*15*). As an example, Toi *et al*. provide results that suggest that neurons in superficial layers of mouse somatosensory cortex are hyperpolarized in response to the excitation of whiskers before deep and middle layers are activated, providing a glimpse of possible new ways to study the intricate communication between brain areas.

A major technical challenge for DIANA will likely be subject motion. Instead of collecting a series of complete images to follow the signal through time and space, like fMRI does, DIANA collects a series of partial images. This means that the stimulus must be repeated to collect the remaining parts of the image, and any motion that occurs between these time points can introduce artifacts. So far, Toi *et al*. have demonstrated DIANA in anesthetized mice, where motion artifacts are limited. The next major milestone will be to demonstrate that it can work in awake humans. In addition, because DIANA needs repeatable stimuli, it remains unclear whether and how DIANA can be applied to study spontaneous activation patterns of the brain that span multiple time scales. The ability of DIANA to lift the temporal and spatial hurdles that now limit BOLD fMRI holds the exciting potential to reveal the detailed computational mechanisms of mental processing at the fast pace at which it unfolds. ■

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