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Commentary

Causality as a New Paradigm in Brain Science

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The refinement of imaging methods combined with the advent of new tools for manipulating brain activity has allowed tremendous progress in neuroscience research over the past 2 decades. As part of this special issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* on translational imaging techniques, Snyder and Bauer (1) reviewed methods for mapping brain connectivity using hemodynamic-based recordings of brain activity, mainly blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI). This was combined with manipulations of neural activity using optogenetics (in rodents) or transcranial magnetic stimulation (in humans) (1). Their focus was on effective connectivity as opposed to functional connectivity based on temporal correlations in brain activity. In this commentary I discuss how their article highlights an important paradigm shift in neuroscience studies: from correlation to causation. This evolution was made possible by recent technical and technological advances. Unlocking the full potential of this paradigm shift depends upon the establishment of similar causality in the study of neurovascular coupling, by taking advantage of these state-of-the-art tools. In order to achieve this goal, the importance of a dialogue between animal and human research—another point made by Snyder and Bauer (1)—will also be discussed.

As stated by Snyder and Bauer (1), the neural basis of fMRI-based resting-state functional connectivity is still not fully understood. This is a direct consequence of our lack of a causal understanding of neurovascular coupling, the basis for hemodynamic-based measures of brain activity. Hemoglobin acts as an intrinsic contrast agent in both optical (i.e., spectroscopic) and magnetic (i.e., BOLD fMRI) imaging methods. But how and on what spatial and temporal scales specific cell types influence blood flow and oxygen consumption in order to create measurable hemoglobin concentration changes is still unknown. In order to bring hemodynamic-based methods—in particular fMRI—beyond mere mapping toward interpreting neural systems and connections, it is crucial to further our understanding of neurovascular coupling, both in response to external stimulation and in the resting state.

Until recently, studies of neurovascular coupling were limited in terms of both interventions and measurable outcomes, restricting their power to establish causality. The pioneering work of Logothetis *et al.* (2) reported correlations between intracortical electrophysiological recordings and BOLD fMRI in response to sensory stimuli in nonhuman primates. A myriad of pharmacological studies did not provide a definite answer. Messenger-specific effects were observed in vitro but could not be translated in vivo. The advent of optogenetics with precise genetic control of light-sensitive protein expression brought access to direct manipulation of specific cell types in live animals. Advances in multiphoton microscopy and fluorescent probes made it possible to concurrently measure membrane potential or cellular Ca^{+2} (3), single blood vessel diameter and flow (4), and, more recently, blood and tissue oxygenation (5) with all-optical tools. This combination of neural manipulation and measurement technologies makes it possible to design experimental paradigms that can establish the causal processes of neurovascular coupling.

Along the way, such experiments revealed various results that call for caution when interpreting hemodynamic responses as a proxy for neural activity. For example, there is evidence of light-induced arteriolar dilation without neuron or astrocyte excitation (6) and of neuronal types that can cause hemodynamic responses without producing any measurable local field potentials (7). Different neuronal cell types also appear to elicit specific hemodynamic response functions [see Supplemental Figure S4 in Desjardins *et al.* (8)]. Furthermore, despite standard protocols relying on anesthetics to control the state of animals during experiments, it was gradually demonstrated that the multiple effects of anesthesia on neural, metabolic, and vascular activity (9) created significant confounds in studies of neurovascular coupling. Optical and MRI experimental protocols are therefore being adapted to rodents that are awake. A side benefit of these new techniques is the ability to conduct longitudinal studies, allowing for intervention studies on different temporal scales.

Well-controlled studies using such methods will provide a comprehensive description not only of the physiology of the neurovascular unit but also of its relation to noninvasive imaging data that can be measured in humans. This will require combining neuromodulation and direct measurements of blood vessel diameters and oxygen metabolism in rodents with noninvasive measurements that can also be obtained in humans, such as BOLD fMRI, cerebral blood flow, and cerebral metabolic rate of oxygen consumption. The latter can be measured in humans noninvasively using calibrated BOLD approaches.

The crucial importance of a constant dialogue between animal and human neuroimaging studies was also underlined by Snyder and Bauer (1). Such a dialogue must also exist between developers of technology (e.g., engineering researchers) and their users (e.g., neuroscience researchers) in order to tailor technological developments to the current needs of basic science. This is also true between the experimentalist community and the communities of modeling and data science, who can guide experimental designs and improve data analysis. An inspiring example of such a dialogue was given by Gagnon *et al.* (10), in which detailed 3-dimensional images of cerebral vasculature measured with micrometer resolution in

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mice were combined with biophysical models of oxygen advection–diffusion and proton diffusion to simulate BOLD data from first principles.

Fundamental understanding of physiology and pathology can be gained from animal studies, but leveraging those in biomedical applications requires a multidisciplinary effort. In order to move toward personalized approaches in medical diagnosis and treatment, medicine needs to rely on causal relations that are translatable to patients.

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Article Information

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