

Editorials

The road to mapping neural circuits with fMRI: Challenges and advances

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BOLD fMRI has significantly advanced our understanding of human brain function. To further progress in brain science, it is essential to interpret the causal relationships underlying fMRI data, moving beyond simple correlations of brain activity. In this article, current challenges and recent advances in circuit analysis using animal fMRI are presented, along with discussion of their potential implications for human fMRI research.

At the 2024 OHBM Annual Meeting in Seoul, Korea, I gave a keynote talk on my animal fMRI research, and shared my perspective on human fMRI research. Although I was initially involved in the development of human fMRI, I shifted my lab's focus to animal fMRI in the early 2000s to investigate the biophysical and physiological basis of high-resolution fMRI, combining it with invasive approaches. More recently, my laboratory has integrated fMRI with optogenetic manipulations to map long-range circuits across the whole brain, similar to conventional circuit dissection approaches, and has extensively studied cell type-specific neurovascular regulation with these tools. My talk focused on using fMRI to dissect neural circuits, including layer-specific fMRI, whole-brain fMRI with local silencing, and high temporal resolution fMRI. In this article, I would like to share my perspective on the future directions of human fMRI research.

CIRCUIT ANALYSIS BEYOND SIMPLE CORRELATIONS

One of the most significant challenges in the human fMRI community is how to interpret fMRI data beyond simple correlations of brain activity. While correlation analyses reveal potential interactions between brain regions, they do not establish causal relationships. Circuit dissection is a fundamental approach in systems neuroscience, essential for understanding neural processes underlying behavior. However, behavioral information flow occurs within tens to hundreds of milliseconds, whereas hemodynamic-based fMRI responses operate on a much slower timescale of seconds. Although modeling approaches have been proposed to determine effective connectivity among brain regions,¹ their validity for evoked functional networks remains uncertain. This raises a critical question: how can we effectively utilize fMRI for circuit analysis?

In the animal fMRI community, fMRI-based approaches for circuit dissection have been evaluated using well-established circuit models, such as sensory pathways. For ex-

ample, sensory information is transmitted to the primary sensory cortex via the thalamus and subsequently propagates to higher-order sensory regions. These models can be combined with electrical, optogenetic or chemogenetic manipulations to locally perturb neural activity,^{2,3} allowing researchers to validate the effectiveness of proposed fMRI methods. Current approaches include layer-specific fMRI, fMRI with local perturbation, and potentially ultrahigh temporal resolution fMRI.⁴ How can these animal studies be translated to humans?

Layer-specific fMRI can identify synaptic input layers within the cortex, allowing differentiation between thalamocortical and corticocortical inputs.^{2,3} This approach has gained traction in human research,⁵ as evidenced by many presentations at the 2024 OHBM meeting. In conventional gradient-echo BOLD fMRI with laminar resolution, signals from intracortical veins draining from deep cortical layers to the pia, as well as from pial veins, can contribute significantly. As a result, layer-dependent BOLD signal intensity may not accurately reflect underlying neural activity, necessitating deconvolution of draining effects.⁶ Alternatively, microvessel-specific fMRI approaches—such as spin-echo BOLD, CBV-weighted VASO, and CBF-weighted ASL—can be employed to mitigate these confounds, albeit with lower sensitivity. With advances in fMRI technology and the increasing availability of ultrahigh-field human MRI, layer-specific fMRI will play an expanding role in complementing whole-brain high-resolution fMRI to provide deeper insights into neural circuits. In particular, it provides a powerful means of distinguishing whether cortical activity is driven by thalamocortical or corticocortical inputs.

One common criticism of layer-specific fMRI is the challenge of resolving input layers, given that interlaminar neural processing occurs within just a few milliseconds. This neural activity-centric perspective has hindered the widespread adoption of layer-specific fMRI within the neuroscience community. However, in recent studies from my laboratory,⁷ we found that excitatory neuronal activity dri-

ves somatostatin interneuron activation, which in turn stimulates astrocytes and elicits hemodynamic responses. While these processes are relatively slow, they are relatively specific to input layers. I believe our findings offer insight into the cellular origins of laminar-specific CBV responses. However, layer-specific fMRI does not directly reveal upstream or downstream regions involved in information flow. Therefore, combining laminar fMRI with complementary techniques such as electrophysiology, or causal perturbations (e.g., optogenetics, chemogenetics) will be essential for a more comprehensive understanding of cortical circuit dynamics.³

A key question moving forward is whether human fMRI can be combined with local neural activity modulation. Noninvasive techniques such as transcranial magnetic stimulation and ultrasound deep brain stimulation offer potential solutions. Our next step is to use fMRI to target functional sites and modulate neural activity in these regions during scanning with neuromodulators—essentially mirroring local silencing experiments in animal studies. Several critical issues must be addressed for the successful implementation of neuromodulators: (1) How effectively modulators can reduce or enhance local neural activity, (2) the precision of neural modulation in terms of spatial and temporal fidelity, and (3) the integration of these sophisticated technologies into ultrahigh-field MRI environments.

The less likely, but highly desirable, solution for circuit analysis is to utilize temporal information from ultrahigh temporal resolution fMRI. Since direct measurements of neural activity via fMRI have not yet been convincingly achieved, my focus remains on hemodynamic-based fMRI. This temporal approach has been employed to measure neural information flow on the scale of seconds, as seen in studies involving delayed motor tasks, delayed sensory tasks, and mental rotation.⁸ However, most neural processes occurring on the scale of tens or hundreds of milliseconds are beyond the typical temporal resolution limits of fMRI. One potential strategy to overcome this limitation is to assess the onset timing of capillary responses across active regions, which may reflect the sequence of neural information flow. This concept has been validated in anesthetized mouse studies using 15.2T MRI,⁴ but it remains uncertain whether current human fMRI technologies can detect the precise timing of microvascular responses. Investigating this question in well-established sensory circuit models could provide valuable insights and help bridge the gap between neural dynamics and hemodynamic timing.

IMPROVING FMRI INTERPRETATION THROUGH NEUROVASCULAR COUPLING

One important question is how to interpret fMRI signals in relation to neural activity. It is often assumed that an increase in the fMRI response reflects excitation, while a

decrease reflects inhibition.⁹ This assumption is generally valid, based on the premise that excitatory neurons, which make up the majority of neurons, are the primary drivers of hemodynamic responses. However, BOLD fMRI studies involving the activation of inhibitory neurons have shown diverse temporal patterns at the stimulation site, depending on stimulation parameters and the specific inhibitory cell types involved.^{7,10,11} In contrast, downstream regions typically exhibit the expected negative BOLD responses.^{7,10,11} Ongoing research is further investigating these cell type-specific modulations in greater detail.

The excitation–inhibition (E:I) balance is a critical index of brain function and is implicated in various psychiatric disorders. A key question is how to gain insight into E:I imbalance using noninvasive methods. Although still preliminary, we propose an approach that combines fMRI with stimulation at varying frequencies to probe E:I property.¹² Excitatory and inhibitory neurons exhibit distinct temporal adaptation properties and interact to establish a new steady-state condition. High-frequency stimulation may accelerate adaptation, while low-frequency stimulation may not induce significant adaptation. Therefore, analyzing frequency-dependent dynamic fMRI responses, in combination with computational modeling, may provide an estimate of the baseline E:I ratio. To validate this conceptual framework, further systematic studies involving controlled modulation of the baseline E:I balance will be necessary.

SUMMARY

Advancing circuit analysis and detecting E:I imbalance through fMRI represent important research directions for linking neural processes to behavior in both health and disease. Insights from animal imaging studies using invasive techniques can significantly inform and guide progress in the human fMRI field.

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CONFLICTS OF INTEREST

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