

Editorials

Reflections on current trends in functional MRI — The State of the Brain 2025

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Keywords: precision medicine, fMRI dynamics, resting-state fMRI, neurovascular coupling, brain metabolics, brain mapping, biophysics, education, brain stimulation

<https://doi.org/10.52294/001c.157595>

Aperture Neuro

Vol. 6, Issue SI 3, 2026

This invited contribution to the State of the Brain series is a commentary on advancements, opportunities and challenges that have been emerging in brain mapping and were highlighted at the educational courses and in the keynote lectures of the Organization for Human Brain Mapping (OHBM) 2025 Annual Meeting. Functional magnetic resonance imaging (fMRI) has been a major driver of progress in brain mapping over the past years, and has continued to furnish us with new tools, new insights and new questions. In my capacity as Education Chair, I will summarize some of the highlighted techniques at this year's meeting, but also the unanswered questions that will be dogging these techniques, particularly in terms of their biological interpretations. By extension, I will discuss the potential impact of fMRI-based brain-mapping tools for the rapidly growing topic of precision brain stimulation. In these regards, I propose that the investigation into the brain's physiological underpinnings, beyond what is currently offered by big-data fMRI, needs more attention from the OHBM community if fMRI is to realize its full potential in neuroscientific and clinical discoveries.

INTRODUCTION

The Organization for Human Brain Mapping (OHBM) is more diverse than ever, in terms of technical advances and access to multi-modal databases, but a major driver of neuroscience and brain-mapping research has been functional magnetic resonance imaging (fMRI). I will discuss three fMRI-related topics that I think have strong relevance to the future directions of brain mapping.

THE IMMENSE POWER AND LINGERING CONUNDRUMS IN RESTING-STATE FMRI DYNAMICS

In addition to the commonly adopted functional connectivity (FC), co-fluctuations in the resting state (rs)-fMRI signal have produced numerous metrics (and a constantly growing lexicon) that have demonstrated immense interest and power, and many of these have been topics of keynote lectures at OHBM 2025 and were presented at the educational course titled “Modes, Components, Gradients”, organized

by Alex Fornito and Daniel Margulies. An FC gradient describes a continuous axis of functional specialization and organization across the brain, especially the cerebral cortex.¹ FC gradients are a way to visualize the hierarchical organization of the brain by using dimensionality reduction to find continuous axes along which FC changes. These gradients represent the brain's organization from simple, direct sensory processing to more complex, abstract cognitive functions. Modes of FC relate to the brain's intrinsic, fluctuating patterns (or networks) seen in rs-fMRI, often identified via independent-component analysis, revealing large-scale network organization and changes over development or disease. These “modes” are essentially the brain's natural operating states, revealed by statistical patterns in spontaneous activity.² In contrast, quasi-periodic patterns (QPPs) are recurring, large-scale brain activity patterns that involve the coordinated, wave-like interplay between the default-mode and task-positive networks. These patterns show alternating activation/deactivation (anti-correlation) and are a fundamental source of the dynamic FC observed in the resting brain, reflecting intrinsic neural processes.³ Closely related are intrinsic modes of rs-fMRI,

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revealed by principal component analysis, a “repertoire of modes” in which transient oscillations organize with fixed phase relationships across distinct cortical and subcortical structures.⁴ Moreover, large-scale dynamic causal modeling (DCM) has been applied to infer effective connectivity (directed, causal influences) from fMRI dynamics, a method that moves beyond correlation-based FC to build biophysically plausible generative models of brain function.⁵

While dynamics provide interesting patterns that may correlate with markers of cognition or vigilance, we need to better understand the sources of temporal patterns. Do they stem from neuronal activity or physiological processes? Do they stem from hemodynamics or cerebrospinal fluid (CSF) dynamics (as discussed later)? In my view, a promising emerging approach to elucidating the nature of “brain networks” is optogenetics. Optogenetics are a neuromodulation technique that uses light-sensitive proteins, can be combined with fMRI to measure whole-brain activity in animal models.⁶

Furthermore, in our past work, we have demonstrated the systemic and vascular influences of rs-fMRI that undermine its neuronal interpretation,^{7–15} which are not always easy to address. Indeed, at times these influences should not be removed.^{10,16} This remains an ongoing subject of knowledge renewal in the OHBM community. These topics are also summarized in our recently published book,¹⁷ in which Catie Chang and I, as editors, sought to provide a holistic overview of the landscape of rs-fMRI dynamics. Thus, despite these biophysical and methodological complexities, as well as the need to constantly refresh the lexicon, I believe rs-fMRI will only grow more widely used.

WHAT IS THE ROLE OF FMRI IN PRECISION BRAIN STIMULATION?

The future of neuromodulation is being defined by a multidisciplinary integration of advanced technology and personalized medicine, moving beyond generalized treatments toward individualized, closed-loop systems. Computational models can provide important insights into the design, operation, and clinical application of neurostimulation tools.¹⁸ For example, in transcranial magnetic stimulation (TMS), field modeling represents a major advance that has yet to be adopted across the majority of studies. In emerging stimulation techniques such as focused ultrasound, fMRI has fed brain models to understand the effect of focal sonication on brain networks,¹⁹ work that was presented at OHBM 2025. However, modeling the target and response has several key limitations related to modeling uncertainties, biological complexity, and practical application. In our own work with photobiomodulation, another emerging form of brain stimulation, we found that modeling does not always reflect in vivo outcome.^{20–22}

In this context, fMRI is frequently used for validation and personalization of brain stimulation methods,²³ and its continued role was showcased at the “Brain Stimulation” educational course at the 2025 OHBM meeting, organized by Hamed Ekhtiari, Robin Cash, Andrew Zalesky and Nicole Peterson. Personalized stimulation is important be-

cause it acknowledges and addresses the substantial variability among individuals in their anatomy, brain function, and responses to stimuli. Personalization can ultimately lead to more effective and consistent outcomes, as well as a reduction of negative side effects or negative findings in brain stimulation.

In a relatively small number of studies, instead of using atlas-based targeting, fMRI has been used to identify personalized targets.^{24,25} Moreover, FC changes have been used to gauge the effectiveness of TMS. A pivotal finding demonstrates that the clinical efficacy of repetitive TMS for major depressive disorder is significantly improved when the target is personalized using fMRI-guided FC—specifically, locating the dorsolateral prefrontal cortex site most anticorrelated with the subgenual cingulate cortex—as fixed, group-average targets are insufficient to account for inter-individual brain architecture variability.²⁶ fMRI FC was also used to follow theta-burst stimulation, suggesting that precise electric-field modeling is essential for predicting and optimizing the neuromodulatory effects of TMS treatments based on individual functional networks.²⁷

fMRI has also been integrated into machine learning frameworks for more powerful closed-loop and personalized neuromodulation. To operationalize this personalization, researchers are integrating multimodal neuroimaging (fMRI and diffusion MRI) with machine learning²⁸ to create comprehensive frameworks for precise target selection, parameter optimization, and treatment response prediction, emphasizing the need for reliable, precise targeting through advanced robotics and computational modeling.²⁸ Moreover, the required computational power for real-time adaptive therapy is being addressed by the emerging concept of neuromorphic neuromodulation, which advocates for ultra-low-power neuromorphic computing architectures to enable sophisticated, on-chip artificial intelligence analysis of neural signals, an essential step for developing truly responsive, closed-loop neurostimulation devices that can continuously adjust therapeutic parameters based on individual neural states.²⁹

In conjunction with the above, precision imaging is gaining momentum in determining the biological basis of brain disorders.^{30,31} Recently, such techniques as dense sampling³² have been used to deeply characterize the dynamic properties of the brain. Dense sampling of individuals over a 28-day menstrual cycle has been used to study hormonal influences on brain function.³³ Moreover, digital twins allow simulation, comprehensive analysis and predictions, as virtual representations of the actual brain. Personalized digital twins could help clinicians see how microscopic changes at the cellular level affect whole-brain dynamics.^{34,35} For instance, virtual brain models to optimize deep brain stimulation in Parkinson’s disease.³⁶ These developments, leveraging multimodal brain mapping, improve the identification of treatment targets in the precision stimulation workflow.

THE NUTS AND BOLTS OF FMRI: STILL UNCLEAR?

Often, we are accustomed to relating higher FC to superior brain function. However, is this always the case? In aging, for instance, both increases and decreases in connectivity have been reported.^{37,38} For one thing, it should be clear that FC as it is usually computed is NOT a map of connections. Thus, is a higher FC better or worse for brain function? It is often not clear. More than that, it is clear that fMRI connectivity depends on broader biological heterogeneity. Alessandro Gozzi's keynote lecture showed that in autistic spectrum disorder (ASD), hypoconnectivity was associated with genes related to synaptic signalling, and hyperconnectivity associated with genes related to the immune system. The marker depends on the biological heterogeneity underlying different ASD models.³⁹ This is an important and novel perspective on the application and implications of how FC is used in clinical studies.

Looking still deeper, the foundation of rs-fMRI is the assumption that neuronal activity is associated with blood oxygenation. The latter, in turn, can be associated with cerebral blood flow (CBF) changes ... or not. Under normal physiological conditions, an increase in CBF (for any reason) will increase blood oxygenation and hence the BOLD signal. In the past, CBF changes have been proposed to be driven by either neuronal signalling directly (feedforward model)⁴⁰⁻⁴² or a need to meet cerebral metabolic rate of oxygen (CMRO₂) needs (feedback model).⁴³ It is becoming increasingly clear that CBF is not purely driven by CMRO₂. One example of this is that even during an artificially induced steady-state CBF elevation, a positive BOLD response was still observed during a visual task.⁴⁴ Another example is that decreases in CMRO₂ can co-exist with an increase in the BOLD signal,⁴⁵ which fundamentally questions the meaning of the BOLD signal. It is also becoming clear that CBF is not purely driven by neuronal activity, as glucose and lactate can both be metabolized directly for synaptic activity.⁴⁶ An example is that the CBF response evolves over time although the level of neuronal activity may not.⁴⁷ Moreover, these models do not explain why the CBF response far outweighs the CMRO₂ response. Thus, other models have been put forth, which suggest other motivations for CBF changes during neuronal activity. Comprehensive reviews and ongoing debates pertaining to the neurovascular basis of fMRI can be found in a recently published volume of the *Encyclopedia of the Human Brain*.⁴⁸

If CBF changes are not strictly tied to CMRO₂ changes, then they could be driven by the need to clear the waste products of metabolism, whether aerobic or not. This is not an entirely new idea,^{43,49} and waste products can be associated with oxidative or anaerobic metabolism (carbon dioxide and lactate, respectively). Relatedly, while both glycolysis and oxidative phosphorylation are critical for brain metabolism, it is commonly believed in fMRI circles that oxygen is necessary for neuronal activity in most cases, and anaerobic metabolism may only be resorted to when oxygen is unavailable.⁵⁰ This, however, is starting to be questioned.⁵¹ If oxygen becomes optional for neuronal activ-

ity, then the premise of BOLD fMRI would naturally shift to the relationship between CBF and homeostasis.⁵² If CBF changes do not necessarily follow neuronal metabolism (energy needs or waste-clearance needs), then CBF changes may not be entirely dependent on CMRO₂ use, and thus the BOLD signal may not accurately reflect neuronal activity in the manner that has been widely believed to date. Recent theories have suggested that, because baseline CBF may be sufficient to supply adequate oxygen to activated neurons, functional hyperemia may instead act to maintain homeostasis and balanced levels of oxygen, carbon dioxide, and pH conducive to metabolism.⁵³⁻⁵⁵ Taken together, perhaps “neurovascular coupling” could be broken down into “metabolic-vascular coupling”, “pH-vascular coupling”, “temperature-vascular” coupling, and so on, allowing us to probe the nature of the BOLD signal in a more focused manner.

Although my early work focused on vascular and metabolic physiology, “physiology” increasingly encompasses more than just these two aspects. It is difficult to miss the recent interest and advances in the use of fMRI to investigate CSF flow, which has links to waste clearance.⁵⁶ Since it was shown that coherent global electroencephalography activity is linked to increased CSF inflow,⁵⁷ the golden age has begun for the CSF, which has often been ignored or even detested in fMRI. For an fMRI researcher, I wondered if brain activity outside of the sleep state can drive CSF flow, and this question was recently answered in part.^{58,59} Moreover, this occurs even on a highly local scale, with sulcal CSF-flow direction changing with the cardiac cycle.⁶⁰ Does this sound like something one could measure with diffusion MRI, which was designed to track microscopic fluid movement?

CONCLUSION

Coming full circle, although brain mapping has existed for decades, the increasing integration of brain mapping by machine learning and bioinformatics is empowering a technological revolution in neuroscience and healthcare. However, the bottom line for me is that our science is only as good as our tools, especially in this age of big data and diverse applications. From the microscope to the telescope, the quality, precision, and scope of scientific understanding, or even of the understanding of reality, are fundamentally constrained and advanced by the ingenuity of the tools we create. The brain-mapping community is diverse, and it is becoming increasingly difficult to grasp all the nuances underlying the myriad of techniques. However, from an educational perspective, I personally believe in invaluable dividends from increasing commitment to multidisciplinary learning of brain-mapping tools, whether qualitative or quantitative.

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FUNDING SOURCES

The author is supported by the Canadian Institutes of Health Research (10.13039/501100000024).

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

Submitted: December 18, 2025 CDT. Accepted: February 09, 2026 CDT. Published: March 17, 2026 CDT.



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