Decoding human brain functions: Multi-modal, multi-scale insights

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Unraveling the intricate relationship between the structure and function of the human brain remains a central and unresolved question in neuroscience. Ethical considerations impose significant constraints on invasive techniques in human neuroscience research. Consequently, knowledge about human brain function often relies on animal models to provide valuable discoveries and insights. However, caution is warranted, as findings from animal studies may not always be directly translatable to humans, especially when investigating higher cognitive functions.

Recent advancements in neurotechnology have enabled systematic efforts to overcome these challenges.[1–3] Multi-modal and multi-scale neuroimaging technologies constitute the fundamental basis for the mapping of structural features of the human brain. Different imaging modalities can quantify diverse biophysical and biochemical parameters related to brain structure, while electrophysiological and optical techniques enable the functional interrogation of neural circuits and networks. The synergistic integration of multi-modal structural and functional datasets across different scales is essential for elucidating the spatiotemporal dynamics and intrinsic connections within this structural-functional continuum. Overcoming intermodal and cross-scale data fusion barriers is a paramount opportunity and priority in neuroscience for facilitating comprehensive brain mapping and decoding neural computations.

It is challenging under current methodological constraints to develop integrative experimental frameworks to study the functions of the human brain across modalities and scales. Most high-resolution histological imaging techniques require brain slicing, leading to the loss of spatial information. While magnetic resonance imaging (MRI) magnetic resonance imaging provides valuable spatial details on the entire brain, its resolution is limited to millimetres, making it challenging to depict the actual brain structure and functional activity. The combination of different modalities collectively provides a more comprehensive insight into the intricate workings of the brain (Figure 1).

The future landscape of neuroscience research is becoming increasingly complex, generating massive amounts of data that pose challenges in storage space when combining different modalities. Therefore, the future of neuroscience

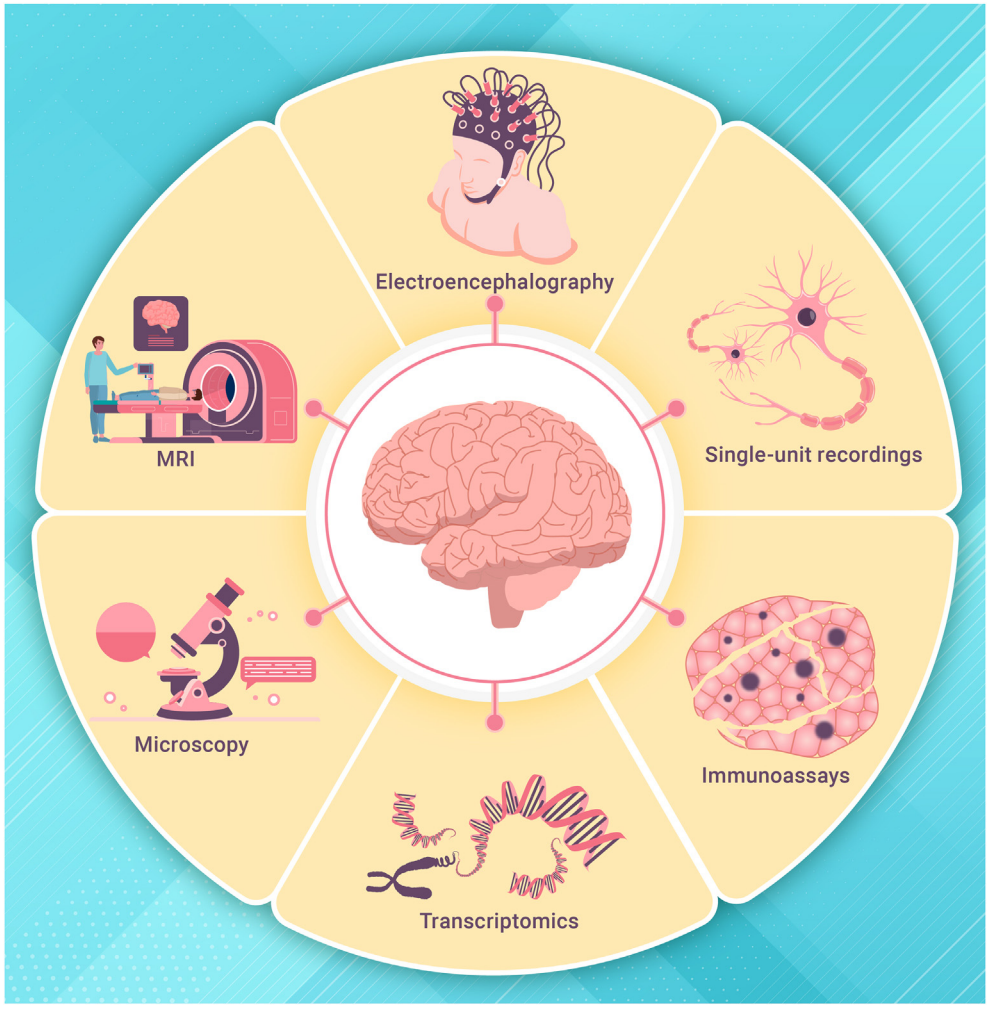

Figure 1. Combining modalities on both micro- and macro scale will help researchers better understand the human brain and all its processes, which we can apply to brain diseases and disorders. MRI can give structural brain information, EEG can show the electrical signals, and electrophysiology allows for recordings of groups of neurons or single neurons, while tissue sections or lysate allow for genetic (e.g., RNA sequencing [RNA-seq] and spatial transcriptomics) and protein expression (e.g., immunohistochemistry and western blot) studies.

research also requires collaboration across diverse fields, involving experts in data generation, complex dataset management, statistics, and unbiased interpretation of results.

Barbosa and colleagues recently showed an elegant way of bridging the gap between neuroimaging data and immunohistology.[4] By integrating data from MRI, histology, and electrophysiology, this study reveals the crucial role of the hypothalamus-hippocampus circuit in appetite regulation. It confirms direct communication between the lateral hypothalamus (LH) and the dorsolateral hippocampus (dlHPC) and delineates projections from melanin-concentrating hormone neurons. This study also observed that people with a higher body mass index (BMI) exhibited reduced connectivity in the LH-dLHPC circuit. However, consideration of subjects used across modalities is crucial, especially when these modalities are applied to non-healthy individuals or abnormal situations, as individual differences may obscure effects. This caution is particularly important when working with neuroimaging data such as MRI, where delineating a brain region, especially a small region, poses challenges due to individual structural differences. Integrating that data across modalities from different subjects also risks introducing imprecise correlations.

The participants included in the electrophysiology study by Barbosa and colleagues have at least one electrode implanted in the hippocampus due to epilepsy. This raises questions about the appropriateness of including patients with epilepsy in a study like this, where the measurements are collected from a diseased brain area and pose the risk of affecting the study focus, i.e., orexigenic projections between the hypothalamus and hippocampus. Despite potential complications, this approach allows electrophysiological studies on specific brain regions, thereby addressing more complex questions than e.g., electroencephalography (EEG) and positron emission tomography (PET) allow. Electrophysiology provides information on connections between brain areas and whether those connections are uni- or bidirectional. Correlating these results with immunohistology can offer valuable information on the cell level, which can be further verified in animal studies, given that the animals have translatability of brain areas, nuclei, projections, etc., to humans.

Even though this is an emerging field, it is fast growing, with anticipated strategy improvements and applications in the next quinquennium. Studies can expand from binge-eating disorders[4] to exploring, e.g., disruptions in the orexigenic projections between the hypothalamus and hippocampus in patients with schizophrenia taking olanzapine.[5] The combination of different modalities is becoming an attractive strategy for studying brain function at micro- and macroscale levels, offering a tool to confirm hypotheses and enhance our understanding of the healthy and diseased human brain. These studies are inherently expandable to other brain regions and diseases, forming a promising avenue for comprehensive exploration.

Integrating different modalities is quickly becoming a strategy to answer questions about how higher cognitive functions and consciousness arise and how different brain regions are involved in various processes. This also makes it possible to envision the construction of a spatial brain atlas that encompasses structural and functional information on both the micro- and macroscale levels. Such atlases provide invaluable insights into disease origination, development, and progression. In addition, they may contribute to improving diagnosis, prognosis, and novel drug targets, particularly in psychiatry and neurodegenerative disorders, where patients are commonly misdiagnosed and prescribed the wrong treatment.

While we are still years away from realizing such brain atlases, the study by Barbosa and colleagues[4] marks the initiation of merging modalities in brain research, foreshadowing their increased application in basic, translational, and clinical neuroscience research.

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DECLARATION OF INTERESTS

The authors declare no competing interests.