Physiology and the BRAIN Initiative

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, guided by recommendations from a distinguished working group and the neuroscience community in BRAIN 2025: A Scientific Vision is a big step forward on the path to understanding the human brain, one of the “grand challenges” of the 21st century (7). The Initiative will support development of new technologies and promote new ways of thinking about the brain. Recommendations target the creation of new tools to classify and tag neuronal and glial phenotypes in different brain regions, to identify their structural and functional connectivity at several scales of spatial and temporal resolution, and to visualize and record the dynamics of their relationships as the brain operates. The report also emphasizes the essential roles of multidisciplinary teams and strategies and mathematical and computational models, as well as the need to enrich training opportunities for the next generation of scientists drawn to the study of the brain and its disorders. Specified metrics will be used to assess progress.

The goals of the BRAIN Initiative follow a trajectory of scientific inquiry and technical developments that can be traced back to the second half of the last century. The advent of accessible laboratory computers facilitated methods for the semi-automated reconstruction of brain microcircuits from electron micrographs of serial sections (10). Advances in neurophysiology included tools for the statistical analysis of spike train correlation dynamics and the introduction of the concepts of “functional” and “effective” connectivity (1)—now widely applied in the study of brain networks—along with optical methods for recording signals from many single neurons simultaneously (5) and imaging of the BOLD signal for non-invasive mapping of brain activity (9).

Fast-forward four decades to the present generation of microscopes, electrode arrays, optogenetics, and other new and emerging technologies that allow the monitoring and selective activation or suppression of specific neuronal phenotypes in behaving animals with unprecedented spatial and temporal precision (2). To note just one example, these approaches have recently illuminated the differential inhibition of thalamic nuclei, adding new support to Francis Crick’s searchlight hypothesis on the role of the thalamic reticular complex in cognition and shifting attentional states (6).

All of this sets the stage for the bold yet pragmatic vision set forth in the BRAIN 2025 report, which clearly articulates many of the obstacles and challenges ahead. Projects already funded under its auspices have been described as “audacious” (7), an appropriate attribute given the mind-boggling enormity of the scale of the methods needed in the coming decades for the acquisition and analysis of data from large networks distributed throughout the brain. The highest spatial resolution in functional magnetic resonance imaging of human brain activity is now on the order of 1 mm. The corresponding three-dimensional volume of a voxel may hold circuits composed of hundreds of thousands of neurons, associated glia, and their intertwining relationships. It is particularly noteworthy that a similar volume of brain tissue (1 mm³) represents the current gold standard for efforts targeting the full three-dimensional reconstruction of microcircuits from consecutive serial sections, although larger volumes are likely on the horizon. In the near term, such efforts will rely on increasingly sophisticated computer algorithms and machine learning, although difficult cases will continue to require tedious human examination, sometimes facilitated by crowdsourcing.

Measurement and perturbation of the millions of neuronal and glial interactions within that same 1-mm³ volume of brain tissue will also require continuing advances in technology. Although visualization of most or all neurons is now possible in some animal model systems and reduced preparations, relatively sparse sampling of microcircuit neuronal activity is likely to be the rule for mammalian brains for some time to come. With denser electrode arrays and optical methods, data acquisition may soon outpace the development of new tools—and the new insights—needed to extract and represent, through dimensionality reduction and abstraction, the coding, flow, storage, and retrieval of information in the brain’s networks.

The Brain 2025 report emphasizes not only the need for higher resolution in human brain imaging but also new tools that noninvasively provide more direct measures of neuronal activity and the dynamics of neurotransmitter release and inactivation. Operations within the brain using neuronal synchrony driven by feedback inhibition and gain modulation by disinhibition, common features of microcircuit architectures, may maintain local metabolic demand generated by synapses and spiking within a tight corridor, potentially obscuring activity by minimizing changes in the magnitude of blood oxygenation signals now used to generate many brain maps. A recent call for papers in the Journal of Neurophysiology further highlights this important topic.

Physiologists reading Brain 2025 may note the omission of the brain stem in the list of brain regions for initial analysis in the mouse and the limited attention given to its vital functions elsewhere in the document. Although perhaps a quibble, this “relative neglect” of the brain stem and some reasons for it have been described recently (8). In addition to its roles in generating sleep and other states of consciousness, hearing, and giving voice to our thoughts, the brain stem is also essential for the control of balance, blood pressure, breathing and defense of the airways, taste, and regulation of the gut with its brain- and immunity-influencing microbiome (4), all of which can be profoundly disrupted with aging, disorders, and disease.

Although there has been and will be debate about specific goals and areas of emphasis in the BRAIN Initiative and other ongoing national and international
efforts, if the past is prologue, there is little doubt that this new “searchlight” on circuits and their dynamics in real and virtual worlds during real and fictive behaviors will accelerate innovation, foster new productive collaborations, and, with hard work and serendipity, bring deep insights into brain mechanisms such as those reviewed in the pages of *Physiology* not so long ago (3).

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REFERENCES


