VIEWPOINT

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Pushing the Limits of Human Neuroimaging

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Since the advent and widespread adoption of computed tomography (CT) in the 1970s and the subsequent development of magnetic resonance imaging (MRI) roughly a decade later, clinicians have increasingly used these powerful imaging technologies to diagnose disease and monitor treatments in myriad clinical settings. None have proven of greater value than in imaging the brain. From initial studies of acute intracranial hemorrhage and defining cerebral neoplasms, understanding diseases of the central nervous system in patients often starts with the superb anatomical images these technologies afford. High-resolution 3D views of arterial and venous vasculature with clear definition of gray and white matter and subcortical/brainstem structures, the ventricular system, dura and meninges, and bony calvarium are available in minutes (with MRI) or even seconds (with CT).

Even though these structural tools are of undeniable utility, in many settings they leave important unanswered questions: will removing a vascular occlusion in the middle cerebral artery leave patients with improved function or put them at greater risk of hemorrhage? Will a plan for aggressive debulking of a glioma prolong survival, or would expanding the procedure leave the patient unable to speak or walk? Similar questions are asked prior to surgery for epilepsy, trading decreasing risk of subsequent seizures with the risks of cognitive deficits. For these questions, the anatomical data are key inputs in decision making (in defining size, location, and extent of structural lesions), but additional information on brain metabolic state, or on the underlying distribution of functional attributes of the brain, is needed.

In other disease settings, including neurodegenerative illnesses such as Alzheimer disease, amyotrophic lateral sclerosis, and others, changes in brain structure are lagging indicators of advancing disease status. Future treatments directed toward the evolving understanding of the molecular pathophysiology have the greatest likelihood of working earlier in the course of disease. The willingness and ability to treat cognitively "normal" patients will require specific companion molecular diagnostics, as well as the means to identify the earliest functional derangements associated with neuronal vulnerability.

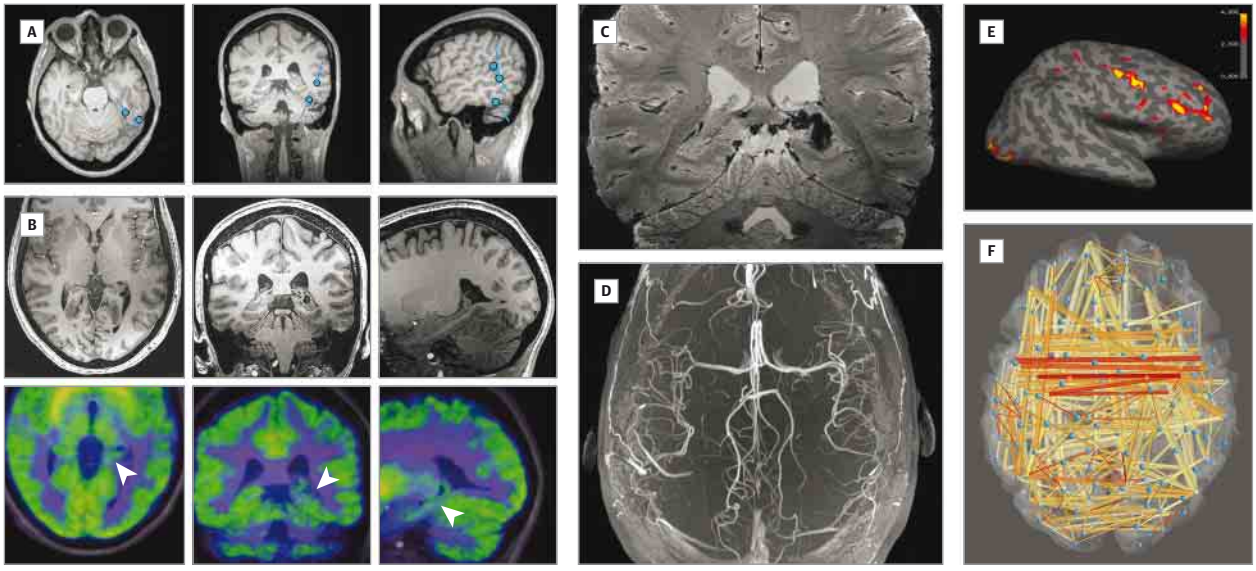
In addition, in many cases of psychiatric illness, no obvious structural brain abnormalities are seen on CT or MRI, despite expressly manifest and potentially devastating behavioral consequences. How can physicians determine which treatments, among several with similar although imperfect efficacy, to select for use for which patients? More fundamentally, in diseases like schizophrenia, which are now thought to represent a heterogeneous array of conditions of uncertain genetic, epigenetic, and environmental origin, what disease does the patient even have?

Several advances in functional neuroimaging technologies offer promising opportunities to answer these clinical questions and to address some of the most fundamental aspects of how the brain works. Several of these imaging technologies revolve around improvements in mapping brain connectivity, both structurally and functionally. Although the ability to map regions of active or eloquent cortex using the association between brain activation and hemodynamic changes (so-called neurovascular coupling) with functional MRI has been known for 25 years,[1] Biswal et al[2] showed that local fluctuations in brain physiologic signals are highly correlated across brain regions organized within functional networks. Recent work suggests that these maps of functional connectivity can provide clear guidance for presurgical planning for resection of brain tumors and epileptogenic lesions.[3] In the future, such maps may allow clinicians to interrogate functionally perturbed networks controlling attention, working and long-term memory, acute or potential threat valuation (fear and anxiety), arousal, and other key cognitive domains, linking behavior with systems neuroscience in organizing and understanding psychiatric diseases and guiding treatment options.

Advances in the sensitivity and resolution of cameras to these subtle physiologic changes should allow analysis of individual patients. Technological advances for neuroimaging, including the use of higher-field MRI systems and dense array coils for routine clinical use, should in the future allow functional connectivity maps to show how information flows from one brain region to the next. Integration of MRI information with other functional modalities, especially those with higher temporal resolution such as electroencephalography and magnetoencephalography, or methods with metabolic or molecular specificity obtained with simultaneous positron emission tomography/MRI systems, will further improve ability to develop a causal understanding of distributed network function and to link circuit function with neurotransmitter and receptor dynamics and trafficking. Further technical advances should allow functional imaging studies to push below the "systems" level (eg, visual, motor) down to resolutions involving the fundamental computational units of brain activity—columns and lamina. At these spatial scales it may be possible to bridge the neuronal circuit-level mapping to the patient level.

These tools for understanding functional networks in patients will be coupled with an increasing ability to map the axonal connections that subserve these networks. Remarkably, despite the detailed

Figure. Advanced Multimodal Imaging in a Case of a 56-Year-Old Left-Handed Woman With Medically Refractory Epilepsy



A, Magnetoencephalography identified a few possible abnormal discharges in the left temporal lobe, shown here as fused images with high-resolution T1-weighted anatomical magnetic resonance (MR) images. B, Metabolic imaging with simultaneous ^{18}F-fluorodeoxyglucose–positron emission tomography/magnetic resonance imaging (^{18}FDG PET/MRI) demonstrated hypometabolism in the left posterior medial temporal lobe. Arrowheads indicate decreased glucose uptake in the left posterior medial temporal lobe. C, Gradient echo MR image obtained at 7 T demonstrated extensive blood products abutting the left hippocampal tail along with a possible large draining vein. D, MR angiography performed at 7 T showed no abnormal vasculature in the left mesial temporal lobe. E, Task-based fMRI for presurgical planning showed right hemisphere activation corresponding to language eloquent cortex. F, Functional connectivity analysis with resting-state fMRI showed decreased connectivity throughout the default mode network in the left cerebral hemisphere. Surgical resection of the lesion in the left mesial temporal lobe demonstrated a thrombosed arteriovenous malformation.

understanding of both the molecular- and cellular-level organization of neuronal circuits that has emerged in the last 2 decades, less is known about the fundamental relationship between the structure and function of the brain than that of any other organ.[4] Indeed, emerging evidence suggests that large-scale motifs in the structural organization of the white matter of the brain have remained hidden until the advent of tools to visualize whole-brain structural connectivity patterns using MRI.[5] In the clinic, images of white matter connections using diffusion MRI tractography are emerging as essential roadmaps for presurgical and even intraoperative planning, while rapid improvements in this technology will allow these structural connectivity tools to be applied robustly and quickly in even the youngest patients. The **Figure** presents an example of advanced multimodal imaging aiding in the diagnosis and management of a patient with medically refractory epilepsy.

New and fundamental insights into the relationships between structural and functional connectivity are likely to emerge, including the links between these properties and patients' underlying genetics, epigenetics, environment, and behavior. In normal populations as a function of life span, later in groups of research participants, and ultimately in individual patients, the ability to understand behavioral diseases at a circuit level suggests an emerging characterization of these disorders as connectopathies arising at any time from early fetal development and childhood (eg, autism), through adolescence (eg, schizophrenia), and into adult life (eg, depression). How to use this knowledge to treat—or perhaps even better, prevent—such disorders is one of the great challenges moving forward. The function of the human brain remains perhaps the greatest biological mystery and the most complex puzzle for science yet to solve.

ARTICLE INFORMATION

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
Dr Huang reported receiving a grant from the Radiological Society of North America.
Dr Stufflebeam reported receiving travel expenses from Elekta Neuromag. No other disclosures were reported.

REFERENCES

1. Belliveau JW, Kennedy DN Jr, McKinstry RC, et al. Functional mapping of the human visual cortex by magnetic resonance imaging. *Science*. 1991;254(5032):716-719.

2. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995;34(4):537-541.

3. Liu H, Buckner RL, Talukdar T, Tanaka N, Madsen JR, Stufflebeam SM. Task-free presurgical mapping using functional magnetic resonance imaging intrinsic activity. *J Neurosurg*. 2009;111(4):746-754.

4. Lichtman JW, Denk W. The big and the small: challenges of imaging the brain's circuits. *Science*. 2011;334(6056):618-623.

5. Wedeen VJ, Rosene DL, Wang R, et al. The geometric structure of the brain fiber pathways. *Science*. 2012;335(6076):1628-1634.