VIEWPOINT

Precision Neuroimaging for Localization-Related Psychiatry

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Psychiatry faces challenges developing into a field in which diagnosis and treatment follow disease models tied to physical substrates. Definitions of illness remain symptom based, with etiological explanations limited to narrative, behavioral, and environmental factors, while brain measurements are used primarily to rule out nonpsychiatric causes. In recognition of this explanatory gap, the National Institute of Mental Health proposed the Research Domain Criteria, which decoupled research into abnormal brain function from *DSM* criteria. The hope is that research into brain mechanisms will reveal biomarkers relevant to psychiatric practice that transcend current definitions of disease.

In neurology, structural imaging and cerebrospinal fluid biomarkers revolutionized understanding of pathophysiology and enabled efficient diagnosis through precise localization of disease processes. Imaging is now a mainstay of neurological assessment. Noninvasive functional brain imaging, including positron emission tomography and functional magnetic resonance imaging (fMRI), has been hailed as a means to capture brain activity associated with psychiatric disease. However, hypotheses about the biological basis of many psychiatric disorders have proliferated,[1] yet functional neuroimaging remains absent from standard practice. Herein, we discuss barriers facing the integration of functional neuroimaging into psychiatric practice and new paths forward that may help overcome these obstacles to usher in a meaningful brain localization–related psychiatry.

Functional Imaging Has Been Too Imprecise for Clinical Psychiatry

To be useful, a biomarker should be reliable (same result with repeated measurements), sensitive (identify pathologic findings when present), and specific (distinguish illnesses from each other). Biomarkers should apply to individual patients and be able to distinguish brain traits (eg, predisposition to treatment resistance) from brain states (eg, depressed mood). These characteristics set the bar high, particularly for functional measures that temporally evolve and depend on state.

Functional imaging is powerful for localizing cognitive operations. However, fMRI has a relatively low signal to noise ratio. Further, fMRI is subject to physiologic (eg, respirations, arterial carbon dioxide pressure) and nonphysiologic (eg, head motion, scanner artifacts) sources of variability, as well as neurally related variability (variations in arousal level) that confound interpretation. These confounders are particularly problematic in resting-state fMRI, which measures functional connectivity (FC) within brain networks and is a dominant method for evaluating whole-brain functional organization. Investigators usually collect small amounts (<10 minutes) of data per patient for a variety of reasons, including limited resources, a presumption that patients will not tolerate more scanning, and a perception that small amounts of data are adequate. To overcome these limitations, data are averaged across subjects to make inferences about brain function. This approach ignores individual variability, generating blurred functional localization of an object that does not exist in nature—the group-averaged brain—and encouraging vague terminology for swaths of cortex (eg, dlPFC [dorsolateral prefrontal cortex]) without functional or anatomical specificity. These limitations form a major barrier to establishing accurate models of brain function and applying functional neuroimaging to clinical practice.

Precision Imaging Reveals New Details of Brain Organization

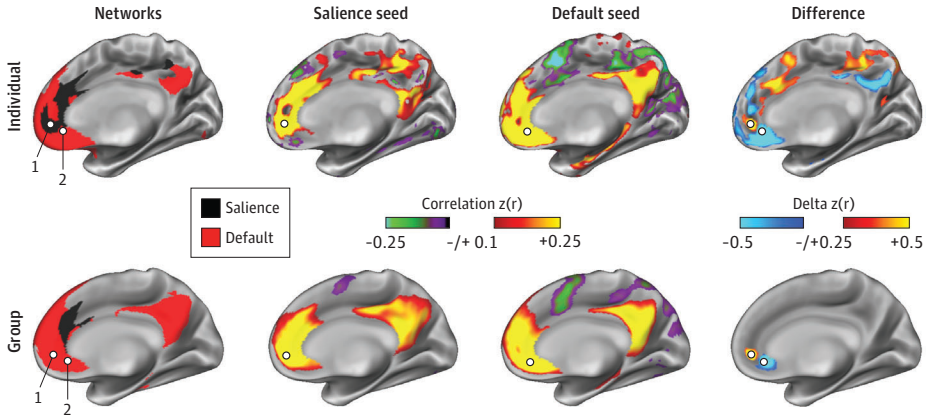
New developments in magnetic resonance sequence design, scanners, artifact reduction methods, and analytic approaches have facilitated novel data acquisition strategies aimed at individual-specific, precise, functional localization.[2] For example, precision functional mapping (PFM), which requires extended and repeated fMRI scans, has identified previously obscured, individual-specific features of functional organization in the cortex, subcortex, and cerebellum.[3] While common patterns of organization exist, individuals also exhibit notable variability in functional localization, including the ventromedial prefrontal cortex, a region frequently implicated in psychiatric dysfunction (**Figure**).

Precision functional mapping has shown that mapping the brain's true functional organization, not the fictitious group-averaged brain, is just beginning. Previously unnoticed spatial interdigitation and subnetwork organization exists.[4] For example, individual-specific data sets reveal that the organization of primary motor cortex is more complex than the classic homuncular model. Remarkably, motor cortex includes previously unrecognized regions with functional connections to control networks and efferents to axial body structures and internal organs.[5] These features implicate underappreciated cortical circuitry in the generation of whole-body physiological states associated with complex behaviors and raise questions about which brain areas are relevant to understanding neuropsychiatric syndromes.

Patient-Specific Functional Localization

If PFM can identify biomarkers associated with psychiatric traits, states, and outcomes within individuals, it should provide several benefits. First, it should confirm whether diagnostically convergent presentations arise from distinct etiologies. Just as acute vision changes can localize to the retina, optic nerve, lateral geniculate nucleus, or occipital cortex, similar psychiatric symptoms may reflect malfunction at different loci of neural

Figure. Functional Network Detail in an Individual Compared With Group-Average Data



Adjacent regions of brain (labeled 1 and 2) in the ventromedial prefrontal cortex exhibit distinct patterns of functional connectivity (FC) that are obscured in group-averaged data. In the group, seeds 1 and 2 would both be part of the default network. In this individual, seed 1 has FC consistent with the salience network, while seed 2 is consistent with the default network.

systems. Conversely, functional connectivity variants may associate with different symptom profiles allowed for by *DSM* criteria.[6] Longitudinal imaging may help distinguish patient-level traits (eg, bipolar disorder) from variable states (eg, elevated vs depressed mood), enabling predictive models of psychiatric functioning. Finally, within-patient PFM imaging designs may clarify systems-level brain mechanisms associated with effective novel (eg, neurosteroids, ketamine, psychedelics) and traditional (eg, serotonin reuptake inhibitors, psychotherapy, electroconvulsive therapy) treatments, including markers of regional plasticity.[7]

Tracking patient-level variability in functional localization has implications for neuromodulatory therapies, such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS). Prior inconsistency in the effectiveness of these treatments may be due to mislocalization of targets. For example, in depression, the exact positions of the subcallosal cingulate cortex target for DBS and corresponding dlPFC target for TMS[8] depend on individual-specific localization of closely juxtaposed functional networks (Figure). Targeting protocols for TMS are being updated to account for such individual differences.[9,10] Results are encouraging, although large-scale randomized clinical trials testing individual-specific network targets vs standard targets have not been reported. Similarly, other technologies for invasive neuromodulation (eg, focused ultrasonography, ablation, intracortical stimulation) should consider individual differences in functional localization to expect success.

Data for precision functional mapping may be difficult to obtain in acute or severe presentations (eg, agitated psychosis). However, PFM is not substantially more demanding than comprehensive structural MRI protocols currently in use. If clinical benefits are clear, costs may be justified. We cannot be certain which aspects of functional representations may be most relevant for psychiatric illness—local regions with loss of function, network-level processing abnormalities, or altered activity from global changes in neurotransmitters. Ascertaining these possibilities requires rethinking traditional data acquisition strategies to enable reliable patient-specific localization through imaging. As advances in neuroimaging progress, new details of functional networks should provide cortical- and subcortical-inclusive, whole-brain models of function. With accurate models, fMRI scans and clinical observations should be reciprocally informative in clarifying pathology. Psychiatrists of the future may need to interpret imaging of brain function as well as they understand interrogations of the mind.

ARTICLE INFORMATION

Published Online: June 7, 2023. doi:10.1001/jamapsychiatry.2023.1576

Conflict of Interest Disclosures: Dr Laumann reported receiving grants from the National Institute of Mental Health during the conduct of the study and consulting fees from Turing Medical outside the submitted work; in addition, Dr Laumann holds a patent for taskless mapping of brain activity licensed to Sora Neurosciences and a patent for optimizing targets for neuromodulation, implant localization, and ablation is pending. Dr Zorumski reported receiving consulting fees from Sage Therapeutics outside the submitted work. Dr Dosenbach reported receiving grants from Turing Medical during the conduct of the study and outside the submitted work; in addition, Dr Dosenbach holds a patent for framewise integrated real-time MRI monitoring licensed to Turing Medical. No other disclosures were reported.

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