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Precision neuroimaging for localization-related psychiatry

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Psychiatry faces great challenges developing into a field in which diagnosis and treatment follow disease models tied to physical substrates. Current definitions of illness remain symptomatic with etiological explanations limited to narrative, behavioral, and environmental factors, while brain measurements are used primarily to rule-out 'non-psychiatric' causes. In recognition of this explanatory gap, NIMH proposed the Research Domain Criteria (RDOC), 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 CSF biomarkers revolutionized pathophysiology and enabled efficient diagnosis through precise localization of disease processes. Imaging is now a mainstay of neurological assessment. Non-invasive functional brain imaging including PET (Positron Emission Tomography) and fMRI (functional Magnetic Resonance Imaging), has been hailed as a means to capture brain activity associated with psychiatric disease. However, after almost 40 years, hypotheses about the biological basis of many psychiatric disorders have proliferated (e.g., [1]), yet functional neuroimaging remains absent from standard practice.

Functional imaging has been too imprecise for clinical psychiatry

To be useful, a biomarker ideally should be reliable (same result with repeated measurements), sensitive (identify pathology when present), and specific (distinguish illnesses from each other). Further, biomarkers should apply to individual patients, and distinguish brain traits (predisposition to treatment resistance) from brain states (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 relatively low signal-to-noise ratio (SNR). Further, fMRI is subject to numerous physiologic (respiration/pCO2 fluctuations) and non-physiologic (head motion, scanner artifacts) sources of variability, as well as true neurally-related variability (arousal-level) that confound

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interpretation. These confounds are particularly acute 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 min) of data per patient for a variety of reasons – limited resources; presumption that patients will not tolerate more scanning; perception that small amounts of data are adequate. To overcome limitations on amount and reliability, 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 use of vague terminology for swaths of cortex ('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 imaging to clinical practice.

Individual-specific precision imaging reveals new details of brain organization

New developments in MR sequence design, scanner improvements, artifact reduction methods, and analytic approaches facilitate novel acquisition strategies aimed at individual-specific, precise, functional localization [2]. This 'Precision Functional Mapping' (PFM), which requires extended/repeated fMRI scans, has identified previously obscured, individual-specific features of functional organization in cortex, subcortex, and cerebellum [3]. While common patterns of organization exist, individuals also exhibit significant variability in functional localization, including ventromedial prefrontal cortex (vmPFC), a region frequently implicated in psychiatric dysfunction (Figure 1).

PFM has demonstrated that mapping the brain's true functional organization, not the fictitious 'group-averaged' brain, is just beginning. Previously unnoticed spatial inter-digitation and sub-network organization exists [4]. New individual-specific datasets demonstrate 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 for psychiatry

If PFM can identify effective 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 retina, optic nerve, lateral geniculate nucleus, or occipital cortex; similar psychiatric symptoms may represent pathology at different loci of neural systems. Conversely, functional connectivity variants may associate with different symptom profiles allowed for by DSM criteria [6]. Finally, longitudinal imaging may help distinguish patient-level traits (bipolar) from variable states (elevated vs. depressed mood), thus enabling predictive models of psychiatric functioning. Further, within-subject

PFM imaging designs may clarify systems-level brain mechanisms associated with effective novel (neurosteroids, ketamine, psychedelics) and traditional (SSRIs, psychotherapy, ECT) treatments, including markers of regional plasticity [7].

Tracking patient-level variability in functional localization has implications for neuromodulatory therapies, like transcranial magnetic stimulation (TMS) or deep-brain stimulation (DBS). Prior inconsistency in efficacy for these treatments may involve mis-localization of targets. In depression, the exact positions of the sub-callosal cingulate cortex target for DBS and corresponding 'dlPFC' target for TMS [8] depend on individual-specific localization of closely juxtaposed functional networks (Figure 1). TMS targeting protocols are being updated to account for such individual differences [9, 10]. Results are encouraging, although large-scale RCTs testing individual-specific network targets vs. standard targets have not been reported. Similarly, other technologies for invasive neuromodulation (focused ultrasound, ablation or intracortical stimulation), should consider individual differences in functional localization to expect success.

PFM-style imaging may be difficult in acute or severe presentations (agitated psychosis). However, it 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, altered activity from global changes in neurotransmitters. Ascertaining these possibilities requires rethinking traditional acquisition strategies to enable reliable patient-specific localization through imaging. As advances in imaging 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.

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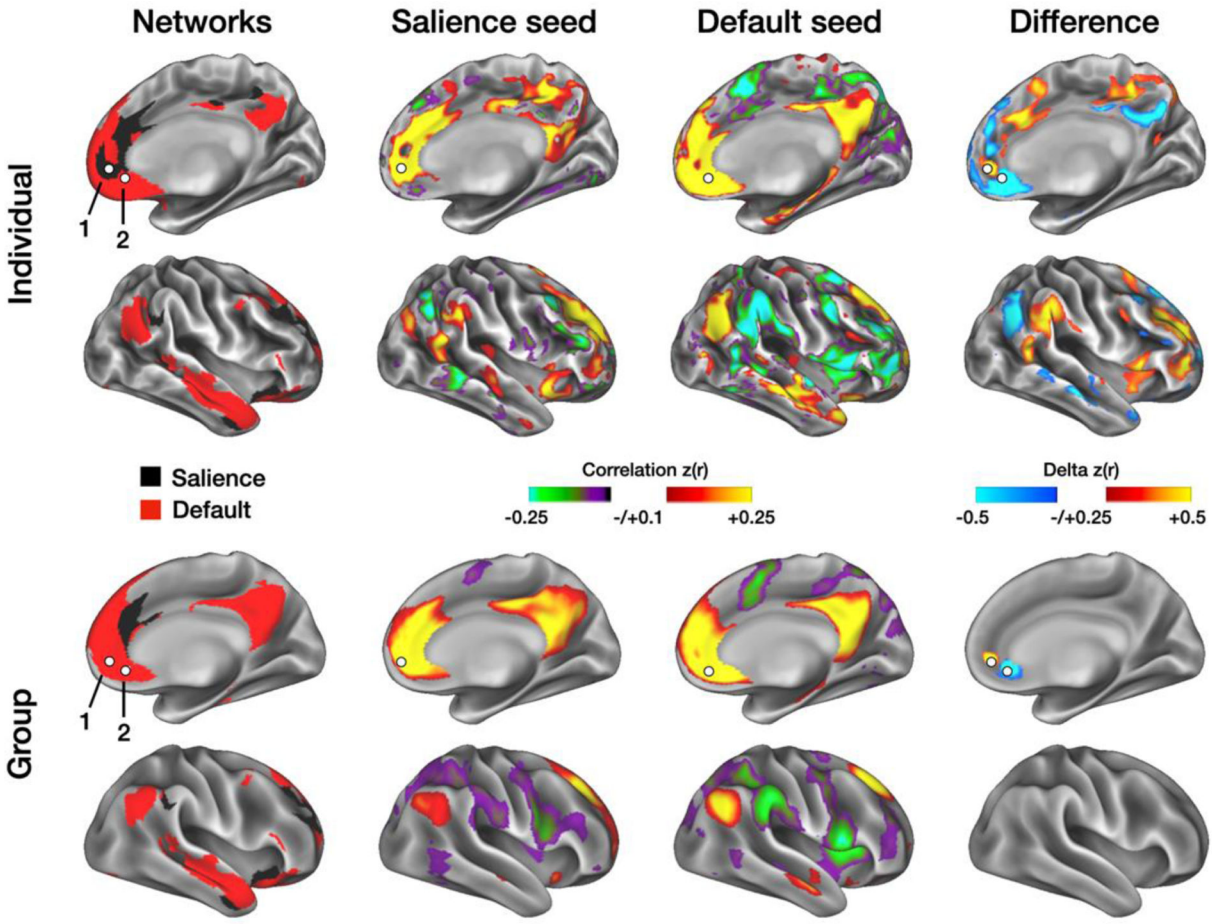

Figure 1.

Functional network detail in individual subject compared to group average data. Adjacent regions of cortex (labelled 1 and 2) in ventromedial prefrontal cortex (vmPFC, which overlaps anatomically with sub-callosal cingulate cortex (SCC)), exhibit very distinct patterns of functional connectivity that are obscured in group average data. In group average data, seeds 1 and 2 would both be labelled as part of the 'Default' network. In this individual, seed 1 has a FC pattern consistent with 'Salience' network, while seed 2 is consistent with 'Default' network.