VIEWPOINT

Tailoring Psychiatric Neuroimaging to Translational Goals

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Psychiatric neuroimaging faces ongoing challenges to establishing reproducible findings and drawing robust inferences.[1-3] Prior standards in sample size, research design, and analysis have all been highlighted as factors in need of potential reform.[1,4,5] Here, we suggest that tailoring psychiatric neuroimaging paradigms toward clear translational and practical end goals is necessary before—and as an ongoing part of—any methodological reform. Instead of relying on universal recommendations for sample size, research design, and analysis, psychiatric neuroimaging should be optimized to suit specific clinically relevant questions across the spectrum of translation.

Brain function varies between and within individuals, changes in response to treatment, and likely has bidirectional relationships with psychiatric symptoms and risk factors. Thus, psychiatric neuroimaging may provide varied clinically relevant insights that ultimately support distinct translational end goals. This includes efforts to advance person-specific mental health diagnostic or symptom screening ("clinical prediction") and those aiming to understand fundamental mechanisms of mental health to identify future intervention and prevention targets ("mechanistic inference"). Historically, however, methodology has not been differentially tailored to support these goals.

The high cost and technical challenges inherent in neuroimaging have led many studies of mental health to rely on relatively small samples (eg, N < 100), cross-sectional observational designs, and focused analyses of a single or very few brain regions or networks.[1,3-5] Yet, large-scale studies have increasingly identified challenges to the statistical power, reproducibility, and validity of this current "standard" paradigm.[1,2] An emerging consensus likewise acknowledges a current lack of biomarkers for most diagnostic categories or symptoms.[1-3] There may be ongoing uses for this standard psychiatric neuroimaging paradigm to generate hypotheses, particularly with improved phenotypic and imaging reliability and validity. However, long-term clinical utility requires hypothesis testing and validation that support clear translational end goals.

With current data collection costs and challenges to reproducibility, not all studies can (or should) support all translational goals. Instead, methodology should be determined by the research question and target of inference (assisted by a practical, translational end goal), rather than resource constraints or the inertia of a previously standard paradigm. Aligning psychiatric neuroimaging to clear translational end goals requires moving to increasingly specialized designs better suited to test specific clinically relevant research questions.

We highlight complementary paths forward for psychiatric neuroimaging in (1) large population-level studies most aligned with the translational goal of clinical prediction and (2) smaller, targeted-sample longitudinal and interventional studies most aligned with the translational goal of mechanistic inference. Neuroimaging may likewise be used to advance other goals across the full spectrum of translation. Further, there are common methodological advances that are necessary for all translational goals (eg, improving measurement reliability and validity,[6] using new methods for phenotyping and image acquisition). Together with common methodological advances, tailoring psychiatric neuroimaging to translational goals will focus resources and accelerate clinical utility.

When developing neuroimaging-based diagnostic or symptom screening for clinical prediction, our methods must maximize the magnitude and generalizability of this prediction. Optimal clinical prediction would likewise not just clarify current diagnostic and symptom presentations (postdiction), but rather predict longitudinal course or treatment stratification. As part of a suite of clinical indicators for screening, this use of psychiatric neuroimaging should be deployable at scale across settings and samples (eg, high risk for depression in various sites) and most likely with a single time point assessment for practical feasibility. Despite such aims, many psychiatric neuroimaging studies have relied on small sample sizes and convenience sampling that undermine this requisite statistical power and generalizability. Large-scale replication studies[1,2] further reveal that current approaches explain relatively small amounts of variability in cross-sectional psychiatric outcomes, have high degrees of imprecision, and lack clinical utility. We suggest that methods to boost effect sizes, improve precision, and ultimately facilitate real-world clinical screening should include (1) recent precedents from neuroimaging[1,4] (as in genomics and public health) of moving to the use of larger sample sizes (eg, thousands of participants) and (2) using increasingly sophisticated whole-brain, multivariate prediction techniques. These efforts will be supported by adherence to best practices for replication both internally (to an independent set of data from the same sample) and, critically, externally (to a new fully independent sample).[1,4]

Even with such advances, clinical prediction–focused psychiatric neuroimaging faces ongoing challenges of diagnostic heterogeneity, sample generalizability, and sociodemographic and cultural biases that are embedded in many population-level analyses. Efforts to address these concerns include using population-representative and equity-informed sampling procedures,[7] optimized and multi-informant phenotypic assessment, and data-driven exploration of diagnostic heterogeneity and transdiagnostic processes. These are substantial methodological challenges, but we believe they are ultimately addressable, particularly through new large and continuously growing consortia, poten-

tial integration with health care system data, and cross-study aggregation and harmonization efforts.

Unlike clinical prediction studies that often start with existing individual-level diagnostic or symptom measures as the "to-be-explained" target, mechanistic studies can help determine fundamental relationships between neuroimaging metrics and mental health. Such studies often rely on groups of individuals with similar features (eg, patients with a specific mental health presentation) and establish future targets for more direct prevention or intervention. To support mechanistic inference, we suggest these types of studies aim to maximize insights into the directionality and potential causality of links between neuroimaging metrics and mental health outcomes. This goal emphasizes the utility of longitudinal and/or intervention-based (eg, transcranial magnetic stimulation, psychosocial and pharmacological treatments) designs[5] that are well suited to establish temporal precedence and increase validity. Owing to the complexity of such designs and the high costs of neuroimaging, studies supporting this goal will often have smaller sample sizes. However, statistical power—and therefore reproducibility—is strengthened through reduced measurement error afforded by repeated assessment and the estimation of potentially larger within-person effects (compared with between-person effects) that can be identified in longitudinal studies. Larger effects may be particularly apparent when the longitudinal assessment period captures a common significant biological change (eg, development, aging) or clinically relevant change (eg, treatment).

An established approach from psychiatry that can support mechanistic inference is a randomized clinical trial design. Extensions of this design (termed by the National Institutes of Health, a "mechanistic clinical trial") that aim to understand the mechanism of action of a clinically relevant intervention (rather than treatment outcome alone) may be particularly well aligned with this translational goal of psychiatric neuroimaging. Owing to the smaller samples and focused designs that are likely necessary to pursue this goal, studies examining mechanistic inference may be better suited to focus on well-circumscribed, hypothesis-driven brain regions or networks. Following best practices, such hypothesis-driven work can limit bias through preregistration of outcomes and analyses and independent replication. Identifying longitudinal brain changes that track biologically and clinically relevant effects with research designs specifically tailored to mechanistic inference can better establish a robust basic science in psychiatric neuroimaging that supports future translational efforts.

In summary, methodological reform is essential for improving reproducibility, inference, and long-term clinical utility of psychiatric neuroimaging. The high costs of neuroimaging prevent all studies from pursuing the absolute largest sample sizes, the most complex research designs, and sophisticated modeling techniques. We suggest that psychiatric neuroimaging research, resource allocation, and funding strategies should align with dissociable translational end goals and adopt appropriate, tailored methodological reforms and specialized designs. Clear translational end goals, including complementary aims of clinical prediction and mechanistic inference, together with ongoing methodological advances, will focus resources, improve reproducibility, and accelerate psychiatric neuroimaging toward real-world clinical utility.

ARTICLE INFORMATION

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