Bridging the Gap: Strategies to Make Psychiatric Neuroimaging Clinically Relevant

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How do we make psychiatric neuroimaging relevant to clinical care? Decades of neuroimaging studies have identified a large and growing canon of correlations between biological and clinical measures in psychiatric disorders. Despite this accumulation of knowledge, neuroimaging has yet to change how care is delivered in the clinic. Furthermore, for most common disorders, such as depression and schizophrenia, neuroimaging has not generated useful models of pathophysiology—that is, models that have been validated and that have subsequently given rise to increasingly sophisticated models. How can neuroimaging move beyond this roadblock? A commonly suggested solution involves the use of increasingly large sample sizes combined with increasing the volume of data collected per individual. In this Disruptive Innovation, we argue that this incremental approach is unlikely to succeed on its own. We argue that a critical next step to make psychiatric imaging relevant is to perturb imaging–phenotype relationships to identify causal relationships. We provide an example of how this approach is used to identify a brain circuit responsible for medication-refractory symptoms in schizophrenia. We then provide a roadmap for how this strategy can be applied broadly and, in so doing, advance therapeutics directly informed by neuroimaging.

Broadly speaking, the long-standing promise of neuroimaging in psychiatric disorders is usually conceptualized in two forms: first, that imaging will clarify diagnosis/prognosis and second, that imaging will directly inform new approaches to intervention, specifically by localizing pathophysiology.

Regarding diagnosis/prognosis, while neuroimaging has clear utility in diagnosing and treating neurologic disorders—such as multiple sclerosis, where imaging complements the physical examination—this is not the case in psychiatry. Psychiatric clinics have seen little clinical utility for neuroimaging for several reasons. Existing diagnostic neuroimaging studies generally compare binary outcomes (e.g., differentiating schizophrenia from bipolar disorder) at the group level. This approach does not reflect, however, a realistic clinical scenario where imaging would guide treatment. Rather, we should take an individualized approach to understanding psychopathology. For example, a more realistic scenario would be symptom driven, such as asking if auditory hallucinations are the product of a psychotic disorder, posttraumatic stress disorder, personality disorder, or more than one of these entities. The field has failed to consider the continuum of illness present in psychiatric disorders and failed to acknowledge the gradient of severity within individual patients. To address this, we must identify the systems responsible for symptom severity, including through the use of continuous measures of psychopathology rather than categorical assessments that are unlikely to reflect the underlying biology.

A proposed solution to the irrelevance of psychiatric neuroimaging principally involves collecting more data by accruing larger samples with longer MRI scans and analysis using novel analytic pipelines. Supporters of this approach suggest that intersubject heterogeneity and the low reliability of standard fMRI techniques at the individual level are inhibiting the translation of neuroimaging findings into clinical application. In order to bridge this gap, supporters propose collecting larger quantities of fMRI data in single individuals as opposed to smaller quantities across larger groups, such as by increasing fMRI scan time to >100 minutes in order to reliably image deep structures, such as the basal ganglia and thalamus. An example of this approach includes the Midnight Scan Club, which imaged >20 hours of fMRI data in ten different individuals. It has been proposed that increasing longitudinal scan data would also resolve differences in scanning conditions. An elaboration of this idea is the conjunction of complementary biological data—that is, combining multimodal imaging with gene expression data from the Allen brain atlas or with polygenic risk scores. There is no indication, however, that we are approaching quantities of observational/correlational data that will be sufficient for informing individual-level clinical questions. Furthermore, the increasing complexity of analytic methods can move toward an extreme, hyperdimensional space, where variables lose their direct clinical relevance. For example, graph theoretical measures based on connectome

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information do not provide a direct pathway toward intervention on a circuit. Although these measures may be scientifically interesting, they are challenging to clinically implement. Connectome studies are also highly dependent on image-processing techniques and data quality, which inhibits adoption by the field at large. Accumulating increasing amounts of data per individual will not enable observational studies to establish causal relationships in psychiatric pathophysiology. Thus, increasing amounts of data will not test if the findings will translate into an actionable result in the clinic.

We propose an alternative solution. Specifically, we argue that psychiatric neuroimaging should focus on validation of circuits and systems that provide insight into the disease state. We argue that validation is best achieved through perturbing circuit-symptom correlation to test the causality of such relationships. Such experiments are organized around within-subject comparisons that are more reflective of the individual-level approach that defines psychiatric care in the clinic. This individual-level approach allows for consideration of heterogeneity of psychiatric illness and individual symptom severity. After identifying the brain circuits responsible for psychiatric symptoms, these circuits can then be acted upon in order to validate their causal relationships. The idea of discovering circuits via observational studies and then perturbing them is not a new one. Unfortunately, this approach has been largely neglected. We argue that the approach is a critically important addition to the proposed collection of increasing quantities of observational data.

Observation of circuit differences in patients is only a starting point to understanding pathological networks in mental illness. Tools that selectively modify networks are required to validate links between networks and disease. These tools could include pharmacologic, psychotherapeutic, or neuromodulatory interventions. While pharmacologic and psychotherapeutic interventions could potentially target deep structures, they currently lack the ability to target specific circuits. Thus, neuromodulation may be uniquely positioned because of its capacity for spatial specificity (i.e., the ability to differentially directly activate one network and not another). Multiple modalities of neuromodulation are available, including deep brain stimulation, repetitive transcranial magnetic stimulation (rTMS), and transcranial current stimulation. Among these options, our group has focused on rTMS because it allows for noninvasive focal targeting of individual brain circuits. This feature also allows for variations in individual structural and functional neuroanatomy, thus ensuring an individual-level approach. Critically, this modality holds substantial potential, as recent studies are beginning to show that circuit-based modulation can determine which imaging findings reflect clinically relevant targets that can be engaged to treat symptoms and which are spurious correlations that do not inform treatment.

We propose that if we use neuromodulation to validate potential circuits identified by imaging, we can advance the field to identify novel forms of treatment. Because imaging can reveal more options than can be meaningfully tested with modulation, we should be prudent about target selection and our validation metrics. The discovery of mood regulation with rTMS to the dorsolateral prefrontal cortex (DLPFC) led to the utility of DLPFC stimulation for major depressive disorder. Because that protocol was approved and safe, most TMS studies in other psychiatric disorders have also targeted the DLPFC. This approach has proven unreliable.

Figure 1. Proposed sequence of (1) empirical identification of networks responsible for psychiatric symptoms, followed by (2) neuromodulation intervention targeted to the identified network and (3) longitudinal neuroimaging to measure network and symptom change.
because no one protocol will be generalizable to all diagnoses; more likely, diagnosis and biomarkers will lead to parameter selection for the individual patient. This targeting weakness is highlighted by the more recent studies that have attempted to use network measures as outcomes to link against clinical measures, resulting in inconsistent findings at best, and elusive target selection at worst.12

For the field to be disrupted, we argue that this sequence must be reversed; we should empirically identify the specific networks responsible for symptoms in order to select the best target for circuit engagement (Figure 1). This approach is demonstrated in Brady and colleagues’ 2019 study,13 where we first empirically identified the neurocircuitry responsible for negative symptoms of schizophrenia (e.g., amotivation, anhedonia) based on patterns of connectivity, and then administered rTMS to that specific circuit. In so doing, we observed that rTMS increased resting-state functional connectivity in this circuit (dorsolateral prefrontal cortico-cerebellar) and led to improvements in negative symptoms.13 Indeed, the key to this approach is the sequential combination of circuit identification followed by perturbation of that circuit rather than using either of these techniques in isolation.

Does this mean that neuromodulation is the future for psychiatric clinical intervention? We would argue no. Here we argue that adding circuit perturbation via neuromodulation to observational imaging is a critical step for psychiatric imaging to fulfill its promise of identifying circuit pathophysiology. This target identification would then provide the basis of any number of potential interventions aimed at circuit manipulation. Ideally, these efforts would include interventions that are more scalable and affordable than imaging-based neuromodulation and could include pharmacologic interventions developed for engaging circuit pathophysiology.

In summary, there is an extraordinary gap between the bench and the bedside for psychiatric neuroimaging. Despite the extensive literature of purely correlational imaging studies, few studies validate those findings. This limits the clinical relevance of psychiatric neuroimaging. Bridging this gap is readily feasible, however, with currently available neuroimaging and neuromodulation methods. Our field requires a change in its approach. Rather than accumulating observational studies with increasingly large sample sizes that provide a snapshot of the brain at a single time-point, we should embrace longitudinal imaging with carefully selected, spatially specific, and properly controlled circuit perturbation between two time-points. This approach can be readily implemented, as these technologies are mature and widely available, and there exist empirically derived targets that can be tested. All that is needed is to change our mindset and test the validity of identified brain signals rather than generating ever more of them.

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REFERENCES