Commentary

Biological Psychiatry

Bringing Human Brain Connectomics to Clinical Practice in Psychiatry

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We now have tools to measure human brain connectivity in vivo. Connectomics is the field of research based on the study and analysis of these connectivity measurements. These developments have inspired efforts to bring connectomics to clinical practice in psychiatry, often in the form of diagnostic tests, prognostic indicators, therapeutic predictors, or markers of treatment response. If successful, these efforts would provide psychiatry with the types of measurements and tools that have been valuable in other areas of medicine. Just like emergency physicians might use computed tomography scans to distinguish pulmonary embolism from pericarditis, psychiatrists might use functional connectivity magnetic resonance imaging (MRI) to distinguish schizophrenia from bipolar disorder. Just as oncologists monitor tumor markers to dynamically optimize chemotherapy, psychiatrists might monitor connectivity changes to rapidly optimize an antidepressant regimen.

Unfortunately, despite decades of valiant efforts, connectomics has yet to broadly impact clinical practice in psychiatry (1). There are at least 2 primary reasons for this shortcoming. First, it is challenging to adequately power neuroimaging studies to detect brain–behavior relationships. Many early-stage studies may have used inadequate sample sizes, leading to false positive findings (2). Recent studies show how larger sample sizes improve reproducibility, a prerequisite for clinical use (2). Second, it is challenging to reliably study connectivity measures at the individual level. Repeatedly scanning the same patient under similar conditions does not necessarily yield similar results, highlighting the need to improve test-retest reliability (1). Recent studies have focused on optimizing scan protocols and analyses to improve reliability at the individual level. The future potential of biomarker development depends on the success of these larger studies with improved methods.

In addition to addressing these scientific and technical limitations, the field must also reach a consensus on several conceptual issues. For instance, we may be asking too much of a single technique or test. Connectivity-based biomarkers have been proposed for nearly every psychiatric illness, even though we continue to define and diagnose them with symptom checklists rather than neurobiology or pathophysiology. In other areas of medicine, we rarely expect a single test to diagnose such a wide range of disorders, particularly when disorders are highly heterogeneous, highly comorbid, and difficult to define. These challenges may be partly addressed with large-scale phenotyping, which can reveal clinical patterns beyond conventional diagnostic boundaries (3).

Despite these challenges, there remains hope for bringing connectomics to clinical psychiatry in the near future via an alternative route. Rather than following the "internal medicine" model of imaging as a diagnostic tool, we may find value in the "surgical" model of imaging as a localization and treatment planning tool. An MRI scan may not be able to diagnose the exact type of brain tumor or guide chemotherapy, but it can still guide a surgical approach to biopsy or tumor resection. Extending this metaphor, clinicians may use brain connectivity to better target neuromodulation techniques such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS). In this context, the goal is not to determine whether a particular connectivity value is abnormal—instead, an MRI is used to localize a target based on its connectivity to brain regions that are most relevant to a patient's condition. These regions would be chosen based on the results of a comprehensive psychiatric evaluation, not based on connectivity alterations. For instance, DBS sites intersecting a specific white matter tract are more effective for obsessive-compulsive disorder (4), while TMS sites connected to the subgenual cingulate cortex are more effective for major depressive disorder (5).

The surgical model avoids some of the limitations of the internal medicine model. First, unlike biomarker development, connectivity-based localization has often yielded similar treatment targets across different studies (5). Using appropriate methods, one can even use connectivity to identify brain stimulation targets that show high test-retest reliability at the individual level, potentially enabling personalized treatment targeting (6). Second, treatment targets can be localized even if the disorder is not well defined. Surgeons successfully used imaging to localize malignancies and guide tumor resections long before our modern understanding of molecular diagnostics. Similarly, a common circuit appears to be connected to neuromodulation targets that improve or worsen depression, even when depression is secondary to a neurological disorder (7).

When searching for treatment targets, we can draw inspiration from prior successes in neuromodulation. For instance, because lesions of the left dorsolateral prefrontal cortex were known to cause depression, it was reasonable to hypothesize that TMS of the same region would relieve depression (5). This lesion-based approach was useful because it provided causal insights about brain–behavior relationships. If a particular brain region is causally implicated in a behavior, then modifying that brain region may modify the behavior. However, it is often impractical to directly compare all possible lesions or stimulation sites, which can come in various shapes, sizes, and locations (5).

This challenge can be overcome by using a human connectome database as a wiring diagram of the brain. By

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estimating the connectivity of lesions and stimulation sites, we can simplify the analysis to compare a handful of brain circuits rather than a myriad of potential locations (5). For instance, the most effective TMS and DBS targets for primary major depressive disorder share a common connectivity profile with lesions that cause depression. Even when there is minimal overlap between the lesions and stimulation sites themselves, our wiring diagram unites them based on connectivity to a shared network (7).

If this finding extends to other neuropsychiatric syndromes, it paves the way for deriving new therapeutic targets. By studying the connectivity of stroke lesions that modify any given symptom, we could theoretically identify more effective therapeutic targets for the same symptom. Several recent studies have validated this approach. Connectivity to a circuit identified by lesions correlated with DBS outcome in Parkinson's disease, cervical dystonia, tremor, and tics in Tourette syndrome (5). This can also reveal safer therapeutic targets, as DBS sites that cause cognitive side effects are connected to the same circuit as lesions that cause amnesia (5). Finally, this can be used to explain the efficacy of known treatment targets, as multicenter clinical trials have found that TMS sites that relieve nicotine or alcohol addiction overlap with the circuit connected to lesions that reduce the risk of future nicotine or alcohol use (8). Together, these results suggest that connectome-guided lesion localization might add a clinically valuable layer of information beyond what can be gleaned from lesion location alone.

These targeting studies provide a roadmap for bringing connectomics to the clinic. This principle is becoming increasingly relevant with the emergence of the next generation of neuromodulation techniques, such as accelerated TMS and focused ultrasound. Novel accelerated TMS protocols appear to achieve unprecedented antidepressant efficacy in only 5 days (9). Connectome-guided targeting is an important component of these protocols, along with optimizations in other parameters such as dose and intertreatment interval. As individualized circuit-based targeting becomes increasingly reliable (6), this technique provides a powerful tool for translating new treatment targets to the clinic. Furthermore, MRI-guided focused ultrasound stimulation is an emerging neurosurgical technique for noninvasively creating lesions deep in the brain, which can lead to long-term symptom relief if targeted appropriately (10). A similar technique known as low-intensity focused ultrasound stimulation may achieve similar short-term effects without inducing an irreversible lesion (10). As these tools become more diverse and powerful, we may find increasing applications for connectome-based targeting.

There may be an emerging need for subspecialized training for psychiatrists to learn about the use of connectomics to monitor and modulate neurobehavioral systems. In the short term, it may be adequate to follow the literature and attend continuing education events. In the medium term, choosing the right treatment target will become increasingly complex as we develop new connectome-guided approaches based on each patient's unique neuroimaging features, symptoms, and comorbidities. In the long term, as challenges with biomarker development are addressed, clinical connectomics may begin to extend beyond neuromodulation targeting. Over time, we anticipate that these developments will build toward a novel subspecialty focused on neurobehavioral systems medicine.

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