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Spotlight

Connectomics reconciles seemingly irreconcilable neuroimaging findings

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Neuroimaging studies have reported heterogeneity of regional anatomical localization for the same disease, impeding reproducible conclusions regarding brain alterations. In recent work, Cash and colleagues help to reconcile inconsistent findings in functional neuroimaging studies in depression by identifying reliable and clinically valuable distributed brain networks from a connectomic perspective.

Over the past two decades neuroimaging studies of the same disease have yielded findings with considerable heterogeneity in regional anatomical localization. For example, in depression, task-based functional neuroimaging studies have localized different brain regions during emotional or cognitive processing [1]. Such seemingly irreconcilable findings impede the generalizability and reproducibility of brain abnormalities across studies, creating a significant challenge for clinical practice, including diagnosis and the selection of effective therapeutic strategies. Addressing this issue will be crucial for gaining a deeper understanding of the underlying neural mechanisms of clinical symptoms and holds promise for the development of imaging and connectivity biomarkers for brain diseases.

Considerable efforts have been devoted to resolving the factors that contribute to inconsistent findings in neuroimaging studies of brain diseases. In addition to interindividual variability in sampling, potential contributors to poor reproducibility include differences in recruitment criteria, imaging protocols, and analysis strategies. Currently, meta-analysis offers a powerful technique to overcome these obstacles by identifying a set of regional abnormalities associated with behavioral impairment and case–control comparisons. Conventional coordinate-based meta-analytic approaches in neuroimaging, such as activation likelihood estimation, have identified local structural or functional foci from the published literature on various brain diseases such as depression [1]. However, significant convergent results across previous meta-analyses for a single disease are still lacking, and the heterogeneous findings have constrained generalizable and consistent understanding.

In a recent issue of *Nature Mental Health*, Cash *et al.* [2] propose a novel network-based meta-analytic framework aimed at addressing the seemingly inconsistent findings in coordinate-based meta-analyses of neuroimaging studies in unipolar depression. This framework postulated that distinct spatial loci of neuroanatomical aberrances associated with specific behavioral impairments should be part of the same distributed brain network, which can be identified by connectomic analysis based upon task-free fMRI data from a healthy adult group. Applying this approach to meta-analytic results from 57 functional neuroimaging studies including 99 task-based experimental paradigms (N = 1058), the authors successfully identified highly reliable, distributed brain networks of emotional and cognitive processing that are abnormal in unipolar depression. Furthermore, the identified depression emotion circuit exhibited significant spatial correlations with prior network models derived from independent datasets and methodologies, such as the 'convergent depression circuit' [3]. This work is groundbreaking because it integrates the apparently inconsistent neuroanatomical spatial loci of meta-analytic studies into functionally connected brain networks through a unified connectomic framework, following the notion that the neuropathology of brain diseases is associated with functionally or structurally interconnected circuits rather than isolated foci [4,5].

It is worth noting that a related approach was employed in a previous study using five independent datasets with varying lesion etiologies and post-lesion depression assessments [6]. In contrast to Cash *et al.* [2], who based their framework on local foci derived from meta-analysis, Padmanabhan *et al.* [6] developed their methodology based on heterogeneously distributed lesion locations associated with depression. They recognized a functionally connected brain map with the left dorsolateral prefrontal cortex as its center, and which aligned with brain stimulation targets that were effective in alleviating depression after stroke. These findings, together with recent functional connectome studies based on large, multi-center depression imaging data, effectively drew reproducible population-based conclusions from heterogeneous samples and highlighted several core dysfunctional networks associated with depression, including the emotion, default mode, and sensory-visual networks [7,8].

Crucially, Cash *et al.* [2] further conducted a retrospective analysis to assess the potential clinical utility of the population-based depression-associated emotional network in optimizing individual transcranial magnetic stimulation (TMS) targets. Specifically, they aimed to identify personalized optimal targets in the left dorsolateral prefrontal cortex using individual-specific temporal signals derived from the identified emotional dysfunction circuit, which includes the subgenual cingulate cortex – a key region frequently implicated in negative affect and treatment response

in depression. They showed that better clinical outcomes were associated with a shorter distance between the actual target and the personalized optimal target guided by the aberrant emotional circuit. This provides empirical evidence for the clinical value of using population-based depression-associated brain networks to optimize individualized treatment strategies. Furthermore, compared to the conventional 5 cm rule used in TMS, the Stanford 'accelerated intelligent neuromodulation therapy' protocol, which is based on stimulation of the left dorsolateral prefrontal cortex site with the most negative functional connectivity to the subgenual cingulate cortex, achieved a remission rate of 90.5% in patients with treatment-resistant depression [9]. This protocol also demonstrated better symptom reduction than sham stimulation in double-blind randomized controlled trials [10]. The retrospective results of Cash *et al.* [2] suggest that personalizing brain stimulation targets based on connectivity with depression-associated dysfunctional networks may improve the clinical outcomes of this treatment regimen.

Overall, Cash *et al.* [2] provide an open window for reconciling seemingly irreconcilable neuroimaging findings in brain disease from a connectomic perspective. Several future research directions are worth considering. First, although the connectome-based meta-analytic framework proposed by Cash *et al.* [2] has demonstrated validity in depression studies, its generalizability to other neuropsychiatric diseases remains to be studied. Second, the neuroanatomical, electrophysiological, and metabolic substrates of the distributed functional brain networks remain unclear. Future studies that combine multimodal data, including diffusion MRI, electrophysiological recordings (e.g., electroencephalography, electrocorticography, and magnetoencephalography), and metabolic imaging data (e.g., positron emission tomography) would shed light on the underlying biological mechanisms of disease-associated brain networks. Third, given the interindividual differences and biological heterogeneity of brain diseases, refined brain network models tailored to different categories or subtypes are needed. Finally, longitudinal clinical trials will be necessary to directly evaluate the effectiveness of this connectome-based research framework in improving individual treatment outcomes in patients.

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Declaration of interests

The authors declare no conflicts of interest.

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References

1. Muller, V.I. *et al.* (2017) Altered brain activity in unipolar depression revisited: meta-analyses of neuroimaging studies. *JAMA Psychiatry* 74, 47–55
2. Cash, R.F.H. *et al.* (2023) Altered brain activity in unipolar depression unveiled using connectomics. *Nat. Mental Health* 1, 174–185
3. Siddiqi, S.H. *et al.* (2021) Brain stimulation and brain lesions converge on common causal circuits in neuropsychiatric disease. *Nat. Hum. Behav.* 5, 1707–1716
4. Fornito, A. *et al.* (2015) The connectomics of brain disorders. *Nat. Rev. Neurosci.* 16, 159–172
5. Gong, Q. and He, Y. (2015) Depression, neuroimaging and connectomics: a selective overview. *Biol. Psychiatry* 77, 223–235
6. Padmanabhan, J.L. *et al.* (2019) A human depression circuit derived from focal brain lesions. *Biol. Psychiatry* 86, 749–758
7. Xia, M. *et al.* (2022) Connectome gradient dysfunction in major depression and its association with gene expression profiles and treatment outcomes. *Mol. Psychiatry* 27, 1384–1393
8. Anderson, K.M. *et al.* (2020) Convergent molecular, cellular, and cortical neuroimaging signatures of major depressive disorder. *Proc. Natl. Acad. Sci. U. S. A.* 117, 25138–25149
9. Cole, E.J. *et al.* (2020) Stanford accelerated intelligent neuromodulation therapy for treatment-resistant depression. *Am. J. Psychiatry* 177, 716–726
10. Cole, E.J. *et al.* (2022) Stanford neuromodulation therapy (SNT): a double-blind randomized controlled trial. *Am. J. Psychiatry* 179, 132–141