Finding brain patterns underlying depression: linking functional neuroimaging to symptom subtypes

Image Credit: PixaBay

By Tony Liu

As used in psychiatry today, the labels of depression and anxiety do little to tell us about the biological root of a person's distress. For example, two patients – both diagnosed with depression – may have completely different symptom profiles. One patient may present primarily with excessive rumination and anxiety, while another patient may have a preponderance of sleep symptoms and anhedonia. Though their different symptoms might suggest that different brain regions and neural circuitry have been disrupted, and thus treatments targeting each individual's underlying dysfunction might be effective, psychiatry still lacks the ability to both map symptoms onto specific neural circuits and translate neural circuit insights into treatment decisions.

What would a more precise psychiatry look like? One can imagine that a patient entering a psychiatric clinic could receive, along with the current standard symptom report assessment, a functional magnetic resonance imaging (fMRI) scan. From this assay of neural activity and connectivity, the treatment team might then determine the specific neural circuits whose dynamics appear abnormal. Critically, this can inform a treatment plan targeted at the patient's specific pathophysiology, with the result of a more effective, rapid recovery.

One challenge in this vision of a more biologically-mechanistic psychiatry has been the sheer difficulty in mapping a single patient's high-dimensional neuroimaging scanning data to their disease symptoms. Both healthy and clinical populations show high variability in neural activity and connectivity, making it challenging to claim that certain neural features causally drive depression. Moreover, the sizes of many brain-behavior effects are small, making it difficult to map psychiatric condition with a neural phenotype. A report in *Biological Psychiatry* [1], published by a team led by Dr. Leanne Williams, Director of the Stanford Center for Precision Mental Health and Wellness, addresses some of these challenges. They present a vision and statistical framework in which an individual's "neural circuit score," derived from their fMRI scanning data, can be used to tailor their psychiatric care.

The central hypothesis of the report is that alterations in specific neural circuits are associated with specific symptom profiles. This idea has been an implicit assumption in troves of work looking for the neural circuit substrates of psychiatric symptoms, including the National Institute of Mental Health's Research Domain Criteria (RDoC) framework. Rather than taking a fully unsupervised approach to defining their circuits of interest, the team started from a set of six neural circuits which have been heavily studied and whose dysfunction has been associated with depression and anxiety. For example, the default mode network is a set of brain regions which have been shown to connect in fMRI during mind-wandering and self-reflection. Prior studies have claimed that hyperconnectivity within this network has been associated with pathological rumination.

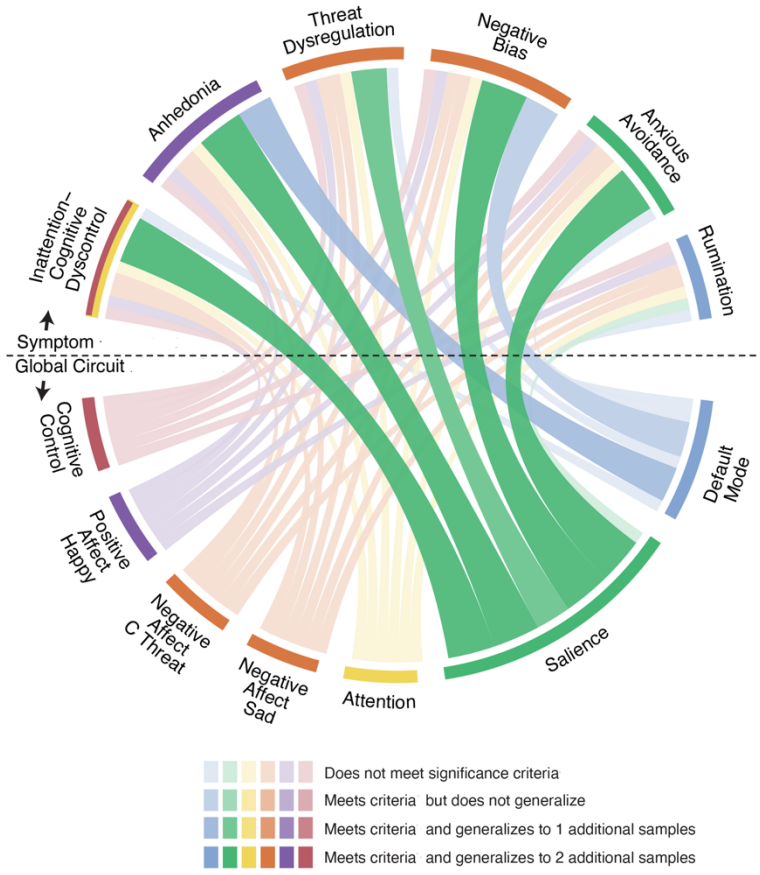
Given the variability in the way different papers define the same circuit, the team specified the regions (sets of voxels) associated with each circuit using both a meta-analytic database and their own dataset of 95 healthy adults. For example, to propose candidate regions in the default mode circuit, the meta-analytic database Neurosynth synthesized the regional activation patterns across thousands of published studies on the default mode network [2]. The team then refined these candidate regions by eliminating those which had stronger connectivity outside the circuit, compared to within it, in the healthy adult dataset. From these select regions, the team then filtered out regions which were not theoretically implicated in depression and/or anxiety-related dysfunction. For instance, though the thalamus passed the initial criteria for inclusion into the "default mode circuit," it had not been implicated in depression or anxiety in meta-analyses or at least two well-powered studies and was thus not included in the final "default mode circuit."

This rigorous selection process led to a final set of circuit definitions, where each circuit consisted of a precise set of brain regions and/or connections between regions. These definitions could then be leveraged to calculate a set of "circuit scores" per patient. In the case of the default mode circuit, the team extracted the pairwise connectivity between each of a patient's anterior medial prefrontal cortex, angular gyrus, and posterior cingulate cortex. The sum of these connectivity values then defined that patient's "global circuit clinical score" for the default mode circuit.

At this point, the authors were poised to map per-individual neural circuit scores to symptom profiles. Given the heterogeneity in psychiatric definitions, the authors correlated their patient derived global circuit scores not with “anxiety” or “depression” broadly, but with more targeted symptom phenotypes, such as rumination and negative bias – whose presence one might more directly attribute to dysfunction in a single circuit.

To influence clinical practice, the knowledge that an individual’s neural circuit score predicts their symptoms is important, but insufficient – the authors also tested whether the neural circuit scores could predict patients’ optimal treatment regimes. On this front, the team discovered intriguing relationships between circuit scores and patient responsiveness to different types of antidepressants or behavioral interventions. Among them was the finding that patients who responded to serotonin versus serotonin-norepinephrine-based antidepressants had significantly different initial default mode network connectivity. To operationalize such a relationship in the clinic, such a result would need to be replicated in an even larger dataset [3].

Taken together, the report by Dr. Williams *et al* demonstrates a methodological framework for taking neuroimaging data and linking it to clinically-relevant outcomes. By synthesizing both theoretical and data-driven approaches to defining neural circuits, and paying close attention to out-of-sample validation, the team sets an important precedent for the field. The practice of openly sharing the initial hypotheses, many of which did not reach statistical significance in the data, is a further testament to the work’s rigorous standard of pre-registration in a field rife with selective reporting of positive outcomes. Further work along these lines may lead to fMRI brain scans having an integral role in personalized psychiatric treatment.



Ribbons indicate a statistical association between a neuroimaging-derived neural circuit (below dashed line) and a clinical phenotype (above dashed line). The thickness of each ribbon indicates the magnitude of the effect size, while the opacity indicates the generalizability of the effect in different sample populations. Image from Andrea N. Goldstein-Piekarski, Tali M. Ball, Zoe Samara, Brooke R. Staveland, Arielle S. Keller, Scott L. Fleming, Katherine A. Grisanzio, Bailey Holt-Gosselin, Patrick Stetz, Jun Ma, Leanne M. Williams, Mapping Neural Circuit Biotypes to Symptoms and Behavioral Dimensions of Depression and Anxiety, Biological Psychiatry, Volume 91, Issue 6, 2022, Pages 561-571, ISSN 0006-3223, https://doi.org/10.1016/j.biopsych.2021.06.024

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