Trends in
Neurosciences

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Spotlight

Toward actionable neural markers of depression risk?

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The search for neural markers of depression remains challenging. Despite progress, neuroimaging results have generally not yielded actionable findings that could transform how we understand and treat this disorder. However, in a recent study, Lynch and colleagues identified enlargement of the frontostriatal salience network as a reproducible, trait-like marker of depression.

The past decades have witnessed a surge of research relying on neuroimaging approaches to characterize psychiatric disorders, including major depressive disorder (MDD) [1]. By probing the structure, function, and connectivity of the living human brain, there was much hope that these approaches would fundamentally transform our understanding, and ultimately treatment, of this prevalent disorder. Despite much progress and many discoveries, it is fair to say that neuroimaging has not transformed clinical care or our ability to identify individuals at increased vulnerability to MDD. There are several possible culprits for this modest progress. First, MDD, as currently defined by prevailing classification systems, is clinically (and most certainly, etiologically and neurobiologically) heterogenous; such heterogeneity has prevented discovering reliable and reproducible neural markers that could be used to guide treatment selection, identify at-risk individuals, or predict mood changes (including future relapses).

Second, with few exceptions (e.g., [2]), fMRI research in MDD has largely paid insufficient attention to individual differences in brain function and structure, and has instead relied on warping individual brains to a common brain atlas. Accordingly, most fMRI research on MDD (and other disorders) has glossed over individual variability in brain function and anatomy that could be clinically informative. This methodological stance is puzzling considering that growing evidence indicates that individual differences in the shape and size of functional brain network are stable over time, heritable, and linked to human behaviors [3–7].

In a recent study, Lynch and colleagues [8] addressed some of these challenges by using a three-pronged approach. First, leveraging resting-state fMRI data, the authors implemented state-of-the-art 'precision functional mapping' to identify the location and size of several canonical functional brain networks. Second, they evaluated a small number of individuals with MDD (N = 6) who were repeatedly scanned (with some individuals scanned up to 62 times). Such dense MRI sampling allowed the authors to identify a substantial expansion of the frontostriatal salience network in MDD and, in particular, to evaluate whether such metric covaried with fluctuating depressive symptoms (it did not). Finally, they relied on three independent data sets to replicate and extend their findings.

Several notable and clinically important results emerged (see Figure 1). First, the frontostriatal salience network was ~70% larger in individuals with MDD. Statistically, this effect was large, as evidenced by the fact that a machine learning classifier using this metric correctly differentiated MDD versus healthy controls with 78.4% accuracy. Such expansion emerged primarily because the salience network encroached other networks, including the default mode network and frontoparietal control network. Given that the salience network is activated by affectively salient information (such as feedback, errors, and reward; e.g., [9,10]), one can speculate that such expansion might be associated with maladaptive cognition and affect (e.g., a reduced ability to cognitively reappraise negative outcomes and/or exaggerated responses to errors or negative cues) that might increase MDD risk and maintenance.

Second, expansion of the salience network had trait-like features: it was stable over time and was not modulated by fluctuating mood symptoms. Critically, salience network expansion also had predictive validity. Specifically, 10–12-year-old children who went on to develop their first episode of MDD 2 or 3 years later were characterized by a 36% larger salience network relative to 10–12-year-old children who did not develop MDD. In other words, this marker identified youth at risk for future MDD. If replicated, this finding might allow us to identify individuals at increased risk of MDD, who could benefit from increased efforts at prevention (e.g., by triggering deployment of cognitive behavior therapy, mindfulness-based stress reduction, or life-style changes).

Third, expansion of the salience network in MDD was reproducible: it replicated in three separate data sets with moderate-to-large effect sizes (Cohen's d = 0.77–0.84). Collectively, these impressive findings point to enlargement of the frontostriatal salience network as a reproducible, trait-like marker of increased vulnerability to depression, which could have important clinical implications.

What might be driving such enlargement? The fact that salience network enlargement was present in youth before the first onset of MDD suggests that this marker is not a consequence of the disorder; rather, it represents a premorbid marker linked to increased risk. Might it reflect increased genetic liability or might it be

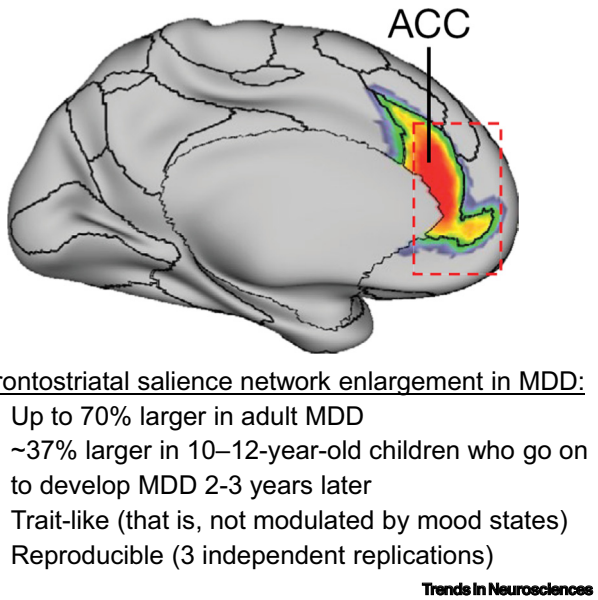

Figure 1. Schematic of the main findings of Lynch *et al.* [8]. The colored region highlights the spatial locations of the salience network in individuals with major depressive disorder (MDD). Abbreviation: ACC, anterior cingulate cortex.

driven by environmental factors known to increase MDD risk, such early life adversity, social determinants, or other factors? To answer the former question, future studies might evaluate whether salience network enlargement is linked to polygenic risk scores for MDD or is present in unaffected monozygotic twins with a depressed co-twin. To evaluate the latter question, longitudinal studies in young children assessed with respect to several environmental factors will be required. Such studies could evaluate whether salience network enlargement emerges gradually with increased exposure to environmental stressors.

Finally, do these findings have clinical implications? As mentioned in the preceding text, if replicated, these findings might be used to identify individuals at increased MDD risk, which could lead to prevention. In addition, could they also point to novel treatments? Might neurostimulation or neurofeedback techniques specifically aimed at constraining the salience network have antidepressant effects and which (if either) is more depressogenic, expansion of the salience network or reduced 'real estate' for other networks, such as the default mode network (critically implicated in self-referential processing) and the frontoparietal control network (important for cognitive control and flexible responding to fluctuating environmental demands)? Addressing these questions would be important goals for future work.

In sum, with their impressive, programmatic, and reproducible findings, Lynch and colleagues have made a key contribution to the field of MDD research and beyond. As with most impactful studies, their findings raise many testable questions. I expect that answering them will bring us closer to using neuroscience to make tangible progress for the many individuals facing this prevalent disorder linked to substantial personal suffering and societal costs.

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Declaration of interests

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