WOMEN'S HEALTH

Toward personalized clinical interventions for perinatal depression: Leveraging precision functional mapping

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Precision functional mapping has the potential to quantify risk of perinatal depression among women through individual-specific neurobiological markers.

THE CLINICAL PROBLEM

Obstetricians and reproductive psychiatrists frequently treat patients who are planning to conceive but who have a history of depression and are taking psychiatric medication with limited or unfavorable reproductive safety data. Patients ask, "Should I continue taking this during pregnancy?" To answer this question, we weigh the risks of continuing such medications during pregnancy against the risks and consequences of the patient developing perinatal depression (PND). PND is a mental health disorder that emerges during pregnancy or in the months following delivery and can include symptoms such as low mood, inability to feel pleasure, feelings of worthlessness, and suicidal ideation (*1*). The consequences of untreated PND include obstetric complications like preeclampsia and preterm birth, lower adherence to prenatal care, and issues extending into the postpartum such as impaired bonding and increased depressive symptoms among children (*1*). PND affects nearly one in five women and is a leading cause of pregnancy-related morbidity, highlighting the urgent need to properly understand and treat this complex condition. At present, we do our best to determine a patient's risk of developing PND based on her history and individual circumstances, but we currently lack quantitative neurobiological markers to help inform these clinical decisions.

Precision functional mapping—a rising methodology that delineates the unique spatial layout of brain networks in an individual, i.e., their personalized functional networks (PFNs)—offers a potential solution (*2*). This technique characterizes person-specific brain features to generate finely detailed neural fingerprints that can be exploited for earlier detection, prediction, and personalized intervention of mental health conditions (*2*–*3*). Applying precision functional mapping to study the maternal brain may both enable the development of quantitative neurobiological markers of risk for PND and optimize personalized neuromodulation (Fig. 1).

PREGNANCY-RELATED BRAIN CHANGES

Over the last 5 years, neuroimaging researchers have quantified the neural changes that unfold during the perinatal period—a time of profound hormonal and physiological change experienced by 140 million women worldwide each year. The standard way to quantify these changes is to compare features of women's brains before and after pregnancy. This body of work has consistently revealed pregnancy-related cortical volume and thickness reductions that are detectable even 6 years postpartum (*4*). Dense sampling designs are now mapping the trajectory of these neuroanatomical reductions across gestation. In a recent study of one first-time mother, brain scans beginning at preconception through 2 years postpartum revealed widespread changes in the brain's gray and white matter occurring in step with advancing gestational week (*5*). This proof-of-concept study demonstrates the value of extensively mapping the human brain over a major hormonal transition period, a nascent but rapidly expanding area of investigation.

Together, these groundbreaking studies demonstrate that areas of cortex that exhibit the greatest structural changes over the perinatal period comprise regions that functionally belong to association networks—networks involved in cognitive, emotional, and social processes. Across association networks, the effects of pregnancy appear most prominent in regions that correspond to the default mode network (DMN), a brain network critical for internally directed cognition and emotional processing (*6*). In their latest work, Paternina-Die and colleagues (*7*) reveal that from late pregnancy to early postpartum, volumetric reductions were most pronounced within the DMN, followed by the attention and frontal control networks. This spatial sensitivity is echoed further in the dense-sampling finding, which shows that controlling for global gray matter volume (GMV) change over the gestational window reveals the strongest effects—i.e., areas of the brain decreasing in volume at a rate greater than the global decrease—within association cortex (*5*). Critically, these areas are also heavily implicated in depression circuitry, with alterations to the function of the DMN, frontoparietal, and salience networks linked to increased depressive symptoms (*6*). While evidence for pregnancy-driven structural changes in areas that correspond to association networks continues to accumulate in normative samples, only a small number of brain imaging studies have included women diagnosed with or at heightened risk for PND, and none thus far have used precision mapping approaches. As such, it is not clear how interindividual differences in association networks present or vary throughout the perinatal period, nor how they relate to risk of PND. This raises several questions: Do preconception differences in these brain networks reflect future risk for PND? Does the extent or pace of functional network reorganization during pregnancy differ in women who develop

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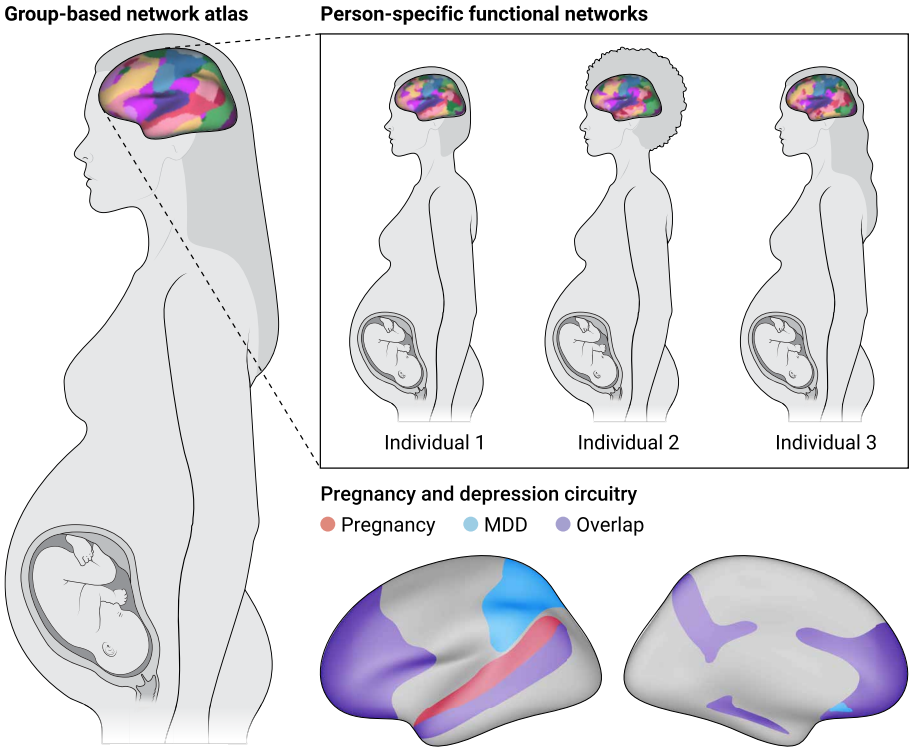

Fig. 1. Mapping the maternal brain. Precision functional mapping may enable the development of individual-specific neurobiological markers of PND risk (*4*, *6*–*7*, *9*). MDD, Major depressive disorder. Illustration credit: Ashley Mastin/*Science Advances*.

PND? Addressing these questions first requires signatures of brain function that are reliable and reproducible at the individual level.

PRECISION BRAIN MAPPING

Since its widespread adoption, functional brain imaging has uncovered foundational mechanisms of brain function and pathology (*3*). However, a major factor that has limited the clinical translation of this technique involves dogma of the most common analytic approach: assuming that functional networks are in the same neuroanatomic location in all individuals. Indeed, by assuming a standard network architecture, we lose meaningful, individual-specific information about the brain's functional organization that shapes information processing, cognitive function, and brain health (*2*–*3*). Ignoring this individual-specific information also introduces heterogeneity in results that hinders replicability and potential clinical utility due to the lack of stable, person-specific metrics.

In contrast, PFNs are defined at the individual level and therefore reflect person-specific functional neuroanatomy. PFNs are both stable and reproducible at the individual level, which increases their potential for clinical translation. Robust and replicable sex differences in PFNs are greatest in association networks including the DMN (*8*), and capturing this specificity accurately predicts individual differences across aspects of cognition and psychopathology (*9*). Indeed, a landmark study published earlier this year showcased the strength of this approach as a potential biomarker for major depression. Using PFNs, Lynch and colleagues identified topographic differences in the salience network among individuals with major depressive disorder, findings that were robust regardless of transient symptoms or treatment (*10*). Most compelling, these network differences were present 2 years prior to the initial emergence of depressive symptoms. Could personalized association networks, especially the DMN, offer the same promise for PND?

ADDRESSING THE CLINICAL PROBLEM: RECOMMENDATIONS FOR FUTURE DESIGNS

We propose that the combined effort of mapping PFNs before pregnancy and longitudinally charting their trajectory through the postpartum in women at heightened risk of PND (*1*) holds the potential to improve medical decision-making for patients with depressive symptoms who are pregnant or planning to conceive. If features of personalized association networks are found to reliably reflect future risk for PND, patients could undergo precision functional mapping as part of preconception counseling evaluations, and this information could be used to inform odds of developing depression during pregnancy and the postpartum.

Such information could eventually be used to build clinically translatable machine learning models that predict an individual's future risk for PND based in part on preconception PFN organization and function. In turn, providers could use these quantitative measures of PND risk to counsel patients in the risk-benefit discussion of whether to continue their psychotropic medications during pregnancy. Regardless of whether this hypothesis holds true, accounting for interindividual variation in the topography of PFNs is essential to minimize heterogeneity in results and for conducting rigorous, reproducible research that accurately accounts for an individual's unique network architecture when studying brain network function over the perinatal period.

We also hypothesize that delineating how pregnancy changes PFNs across the gestational window has the potential to optimize neuromodulation. Specifically, for women with depression who may be on a medication with unfavorable reproductive safety data, transcranial magnetic stimulation (TMS) offers a safe and effective alternative treatment option during pregnancy and lactation. TMS directly stimulates only the outermost layer of the brain. However, recent research has suggested that mapping a person's specific brain architecture may allow TMS to simulate deep brain targets that are involved in depressive circuitry (*11*). Thus, mapping PFNs across the perinatal period may inform and improve stimulation site selection and therefore optimize neuromodulation. Although PFN topography is generally thought to be stable in adulthood, PFNs evolve during sensitive windows such as adolescence (*9*). As we have learned from translational studies, pregnancy is a time of dynamic neuroplasticity with marked changes in brain structure and function (*4*). As such, while preconception PFNs may be important for risk stratification, delineating PFNs across pregnancy would likely be necessary to accurately inform targeted neuromodulation.

While we propose that leveraging PFNs may be key in improving prediction and

treatment of PND, not all functional MRI (fMRI) data are suitable for deriving reliable PFNs. Major considerations and recommendations for using precision functional mapping to better elucidate the neurobiological underpinnings of PND are:

1) fMRI sequences of sufficient duration are necessary to derive stable, reliable PFNs reflective of an individual's intrinsic network topography. For single-echo sequences that represent the overwhelming majority of functional MRI studies acquired to date, the length required is substantial and may range from 27 min to several hours depending on acquisition parameters, analysis methods, and study population (*2*, *11*). In contrast to single-echo fMRI that acquires one image per volume, multi-echo fMRI acquires multiple images per volume. These additional data increase signal-to-noise, improve reliability of functional network metrics, and enable derivation of PFNs with considerably shorter acquisitions—see (*12*) for further detail. Given the potential discomfort and hemodynamic effects of remaining supine for extended periods of time later in pregnancy, leveraging multi-echo sequences will be particularly important in studying PND.

2) The use of standardized, validated image preprocessing pipelines that minimize signal artifact with rigorous motion correction techniques (e.g., 36-parameter confound regression and despiking) are essential in ensuring the reliability of derived PFNs.

3) While the majority of studies that measure brain network organization or function utilize resting-state (e.g., stimulus-free) data, use of naturalistic viewing paradigms during acquisition may further enhance our ability to capture interindividual differences in functional data.

4) Given clinical evidence that sensitivity to hormonal fluctuations frequently manifests across reproductive events in a specific individual (e.g., menstrual cycle, pregnancy, and perimenopause), examining preconception PFN organization and function during both follicular and luteal phases of the menstrual cycle may provide additional insight into an individual's future risk of PND.

Together, these recommendations, paired with the generation of large datasets composed of individuals from diverse populations, will enable researchers to develop machine learning models that use person-specific brain measures to predict an individual's risk of PND.

TOWARD PATIENT-SPECIFIC TREATMENT OPTIONS

Precision brain mapping may help us understand how hormonally sensitive brain networks (e.g., DMN and other association networks) reorganize during the perinatal period and give rise to meaningful differences in one's mental health. However, until standardized protocols for defining, identifying, and analyzing PFNs are developed, it will be important to assess and account for differences in methods and interpretation across studies. For example, existing heterogeneity in both methods used to define PFNs and network nomenclature of derived networks limits integration of corresponding results across investigations.

It is also important to acknowledge that risk for PND does not rely solely on differences in brain function. Other risk factors, including but not limited to immune response, epigenetic markers, health histories, life experiences, and psychosocial factors, will be important to consider when determining an individual's risk for PND (*1*). Robust datasets made up of highly sampled and deeply phenotyped women studied through this period will allow for a more thorough exploration of PND by modeling the interaction of these risk factors and elucidating drivers of brain change. For example, it will be critical to explore the direct and indirect impacts of an individual's exposome on network reorganization over gestation and the downstream consequences for PND risk. Looking forward, precision functional mapping may also be leveraged to better understand and develop interventions for psychiatric conditions that emerge during other hormonal transition periods, such as perimenopausal depression.

Mental health conditions are among the most common and most underdiagnosed complications of the perinatal period and present lasting effects on the mother, child, and family. As such, optimizing clinical interventions for PND should be considered a high priority research area across the neurosciences. Applying precision neuroimaging techniques to the study of the maternal brain may lead to necessary breakthroughs in women's mental health research.

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