Review

Biological Psychiatry: GOS

Precision Functional Mapping to Advance Developmental Psychiatry Research

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ABSTRACT

Many psychiatric conditions have their roots in early development. Individual differences in prenatal brain function (which is influenced by a combination of genetic risk and the prenatal environment) likely interact with individual differences in postnatal experience, resulting in substantial variation in brain functional organization and development in infancy. Neuroimaging has been a powerful tool for understanding typical and atypical brain function and holds promise for uncovering the neurodevelopmental basis of psychiatric illness; however, its clinical utility has been relatively limited thus far. A substantial challenge in this endeavor is the traditional approach of averaging brain data across groups despite individuals varying in their brain organization, which likely obscures important clinically relevant individual variation. Precision functional mapping (PFM) is a neuroimaging technique that allows the capture of individual-specific and highly reliable functional brain properties. Here, we discuss how PFM, through its focus on individuals, has provided novel insights for understanding brain organization across the life span and its promise in elucidating the neural basis of psychiatric disorders. We first summarize the extant literature on PFM in normative populations, followed by its limited utilization in studying psychiatric conditions in adults. We conclude by discussing the potential for infant PFM in advancing developmental precision psychiatry applications, given that many psychiatric disorders start during early infancy and are associated with changes in individual-specific functional neuroanatomy. By exploring the intersection of PFM, development, and psychiatric research, this article underscores the importance of individualized approaches in unraveling the complexities of brain function and improving clinical outcomes across development.

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Psychiatric disorders affect >30% of all youth and can be highly impairing (1–5). Despite many available treatments, >50% of affected children remain symptomatic (6). Risk of psychiatric disorders may be linked to variation in brain function already near the time of birth (7–10); however, the particular sequence of altered neurodevelopment that gives rise to specific mental health problems is not known. Describing this altered neurodevelopmental trajectory linked to psychiatric disorders is complicated by recent work indicating that individuals vary in their functional brain organization (11–13). Here, we propose that the next critical step in the path to developing mechanism-based interventions is to therefore characterize brain-based models of psychiatric disorders that are both developmental and personalized.

Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have made progress in identifying the systems-level neurobiology of various psychiatric disorders. The standard approach has been to collect modest amounts of fMRI data in large groups of individuals, align each participant's brain into a common anatomically defined space (e.g., stretching/compressing each individual's brain until they match in size and shape), and compare affected with unaffected individuals in some functional brain metric defined from this common anatomical space (e.g., resting-state functional connectivity [RSFC] between brain regions, or evoked activity from a brain region in response to specific stimuli). This approach has uncovered differences between affected and unaffected individuals in many psychiatric disorders in adults and children (14–20). Many of these differences have already been detected near birth (9,10), suggesting that the brain bases of many psychiatric disorders may begin early in development.

While this standard group-average approach has been useful, recent work indicates that individuals vary meaningfully in functional brain organization. Precision functional mapping (PFM) is a technique that involves collecting sufficient amounts of fMRI data (often hours) in an individual to precisely and reliably characterize that individual's functional brain organization (21–26). As reviewed in detail below, work using this technique calls into question a basic assumption of the group-average studies that aligning individuals' brains anatomically permits measurement of activity in the same functional brain area across a group of people and characterization of how this area functions differently in a particular psychiatric disorder.

The goal of this review is to highlight how PFM can be used to advance developmental psychiatric research. In the first section, we briefly review the current literature on PFM describing

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heterogeneity in functional brain organization, particularly among systems relevant for psychiatric illnesses. In the second section, we review the current literature on the use of PFM in psychiatric research in adults and describe the specific mechanisms that PFM can uniquely uncover. Finally, in the third section, we outline how PFM can be used to better characterize developmental mechanisms in childhood psychiatric disorders.

PFM HAS ELUCIDATED UNIQUE AND SHARED BRAIN CHARACTERISTICS

The neural bases of cognition, emotion, and behavior are the product of interactions across distributed, large-scale brain networks. The traditional group-average approach to RSFC has revealed many principles of brain organization in humans, such as the shared topology of cortical areas (27–29) and functional networks (30,31). In contrast, PFM has revealed individual-specific features that are obscured by group-level approaches (11–13). These individual-specific features include shifts in the exact location of the boundaries between networks ("border shifts") as well as variants in which some individuals have a portion of a network in a location that is not seen in the group average (inclusions) (32,33) (Figure 1). These individual network variants have been found among nearly all functional brain networks, and they are highly stable over at least a year within an individual adult (12,23,33). Some network variants are common to many people and occur in characteristic locations, often in multimodal association networks associated with higher-order cognitive processes (33). Although further work is needed to clarify the functional implications of network variants, initial work indicates that the presence or absence of variants may relate to individual differences in cognition and behavior (33).

Individual-specific variations in network topography are reliable and cannot be attributed to measurement error, differences in neuroanatomy, motion artifacts, or registration issues (21–23,32–37). Such variations are also highly heritable (38). Furthermore, the locations of task activation obey topographic boundaries of individual functional brain networks (22,23,33,39–41) with higher fidelity than mapping task activation patterns to group-averaged functional networks (32), providing validation of the individualized networks. Individual characterizations of functional brain organization in adults have also been described at the subcortical level including the basal ganglia, thalamus, cerebellum, and amygdala (36,37,42–44). As detailed below, this finding of functional heterogeneity of the subcortex has important implications for prior work that has described group-average subcortical differences associated with psychiatric disorders and for models of psychiatric illnesses that highlight the subcortex (e.g., the amygdala in anxiety, the hippocampus in depression, the striatum in obsessive-compulsive disorder).

Individual differences in functional brain organization are likely to have implications for developing brain-based models

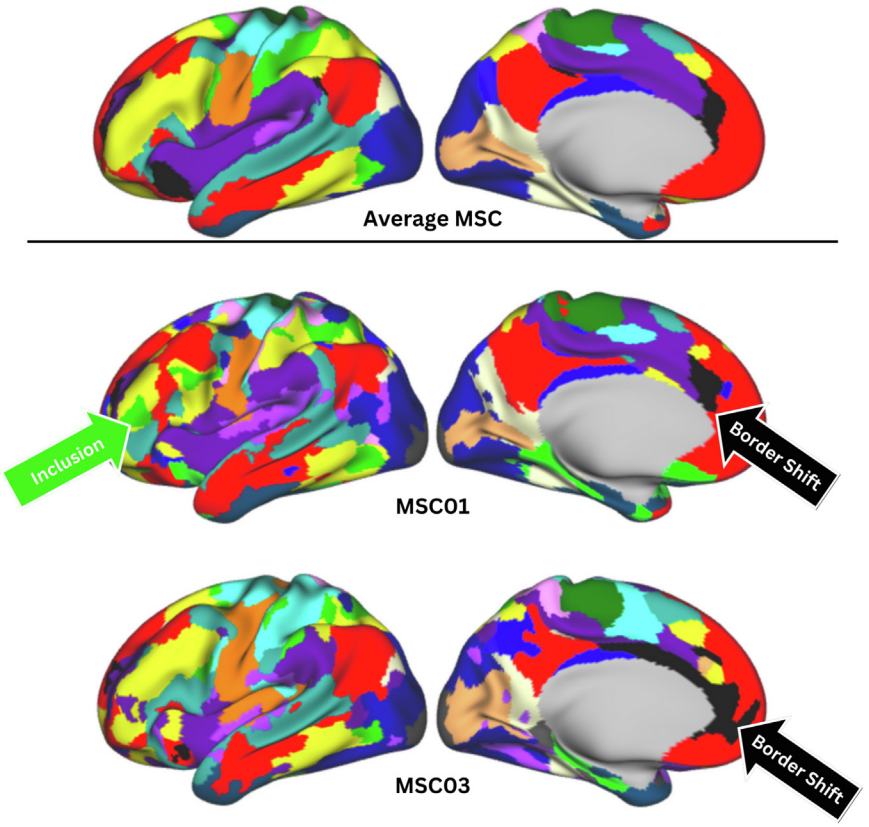

Figure 1. Functional network topography is individual specific. Functional networks identified in group-average data (top) and in 2 individuals (bottom). Network variants are highlighted that are observed across individuals but absent from the group average. In the group average, the inferior frontal gyrus belongs to the frontoparietal network (yellow), but an inclusion (green) is shown in MSC01 whereby the dorsal attention network (green) is present on the inferior frontal gyrus. In both individuals, the salience network (black) shows a border shift (black) compared with the group average. [Adapted from Figure 3 in Gordon *et al.* (32) with permission]. MSC, Midnight Scan Club.

of psychiatric illnesses in individuals. For example, many models of psychiatric illnesses, including anxiety disorders, include disruptions of amygdala function and connectivity (45). However, using PFM, we demonstrated that individuals exhibit substantial variability in functional organization of the amygdala (43). In 10 individuals from the Midnight Scan Club with PFM data, we detected 3 functional subdivisions of the amygdala: one amygdala subdivision was preferentially connected to the default mode network (DMN), another was preferentially connected to the dorsal attention network, and a third had more nonspecific connectivity. Notably, the size and locations of these 3 amygdala subdivisions varied substantially across individuals, consistent with previous results described for variability in the locations and size of cortical networks (32). A consequence of this variability is that measuring RSFC between 2 anatomically defined locations in the amygdala and cerebral cortex will measure different functional areas across different individuals. For example, one hypothesis is that anxiety is associated with decreased RSFC between the medial prefrontal cortex (mPFC) and the amygdala. Current group-average approaches would define anatomical areas in the mPFC and amygdala and compute RSFC between these same 2 anatomical areas in all participants. As can been seen, this approach will capture different functional areas in different individuals—in the mPFC, for example, the same anatomical area captures the salience network (SN), DMN, or other networks in different individuals (Figure 2). However, a PFM approach permits the functional characterization of each individual, such that we can measure RSFC between the same 2 functional areas, even as the anatomical location of those areas varies across individuals. For example, using PFM, we could measure the RSFC between the specific portion of the mPFC that is the SN and the DMN subdivision of the amygdala. This functional characterization is likely to be more useful for psychiatric studies that aim to capture alterations in brain circuits defined based on function (e.g., RSFC, circuit activity) (46), although anatomical features (white matter integrity, subcortical volumes) also provide important mechanistic insights.

A consequence of the results above is that current approaches that use group-average anatomical locations confound variability in the functioning of a functional area with variation in the anatomical location of that area. For example, prior group-average work has linked anxiety to decreased RSFC between the amygdala and mPFC (45,47). One possibility is that this result partly reflects decreased RSFC between 2 functional brain areas, e.g., the portion of the mPFC that is the SN and the DMN subdivision of the amygdala. Another possibility is that this result reflects that individuals with anxiety have, on average, a different functional area present at the anatomical locations measured in this group-average work compared with healthy individuals (e.g., individuals with anxiety tend to have the SN at the anatomical area defined in the mPFC in these studies while healthy individuals tend to have the DMN). PFM can be used to adjudicate these possibilities, clarifying underlying biological mechanisms.

Decades of work and many thousands of group-average studies have associated psychiatric disorders with variation in the RSFC across the cortex and subcortex. While this work has been highly valuable in uncovering the basic systems neurobiology of many psychiatric disorders, the example above illustrates the challenges in interpreting this prior work and calls for the need to supplement these large group-average studies with studies that use PFM to precisely characterize functional locations in individuals.

RECENT WORK USING PFM IN PSYCHIATRY

Here, we focus on the implications of the PFM work described above for characterizing mechanisms and guiding treatments for psychiatric illnesses, as well as examples of studies that have taken this PFM approach in psychiatry. We highlight 3

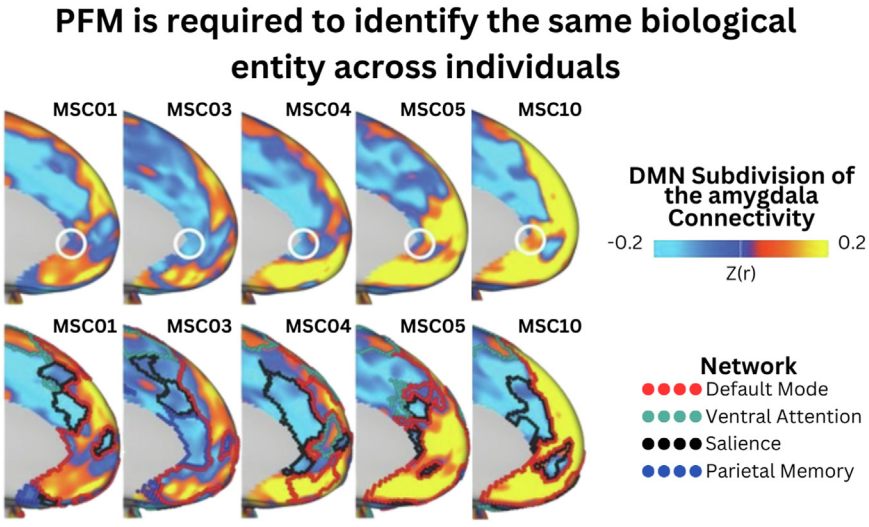

Figure 2. Individual network mapping is required to identify the same functional biological entity across individuals. These maps show the medial prefrontal cortex (mPFC) in 5 individuals scanned using precision functional mapping (PFM). Both panels show the magnitude of resting-state functional connectivity (RSFC) of the mPFC to the default mode network (DMN) subdivision of the amygdala. The white circles in the top panel indicate the same anatomically defined location across all 5 individuals. Note that the magnitude of RSFC within this circle varies substantially across individuals, with some individuals having positive RSFC and others negative RSFC. The colored outlines in the bottom panel indicate network outlines for each individual. Each individual has a consistent pattern of RSFC when considering functional locations, e.g., positive RSFC to portions of the mPFC that are DMN and negative RSFC to portions of the mPFC that are salience network. Standard group-level approaches compare RSFC across individuals in the same anatomical location (the white circle in panel B), confounding variation in RSFC between functional areas with variation in the functional area present at a specific anatomical location. [Adapted from Figure 4B in Sylvester *et al.* (43) with permission]. MSC, Midnight Scan Club.

specific types of mechanisms that PFM studies are uniquely equipped to uncover relative to group-average studies: 1) mechanisms that depend on variation in functionally defined brain areas rather than anatomically defined areas, 2) mechanisms that are caused by differences in functional organization, and 3) mechanisms that vary across individuals with the same symptomatically defined illness (i.e., mechanistic heterogeneity). This section explores these novel applications of PFM for psychiatric research that build upon existing hypotheses as well as provide novel insights into mechanisms of psychopathology among adolescent and adult populations (Figure 3).

PFM can characterize mechanisms that result from alterations in a particular functionally defined brain area. As described above, individual variability in functional network topography implies that measuring RSFC between 2 anatomically defined locations will measure different functionally defined biological entities across different individuals (Figure 3A). Thus, identifying individual-specific patterns of RSFC through PFM will likely be a useful tool for uncovering mechanisms and guiding treatments in individuals for various psychiatric illnesses. For example, models of treatment-resistant depression posit altered activity in the subgenual anterior cingulate cortex (sgACC), potentially resulting from impaired regulation by the dorsolateral prefrontal cortex (dlPFC) that could belong to different functional networks, including the DMN and the frontoparietal network, depending on the individual (50–54). This model is supported by treatment studies that improve symptoms of depression by altering activity in these brain areas, including deep brain stimulation of the sgACC and transcranial magnetic stimulation of the dlPFC (44,50,52,55). Despite the promise of these treatments, efficacy in large-scale clinical trials has been inconsistent (51,56,57), and there is a need for optimizing these stimulation techniques. Some researchers have proposed that the efficacy of transcranial magnetic stimulation, for example, could be improved by stimulating the specific portion of the dlPFC with the highest magnitude of negative RSFC with the sgACC. While there is support for this hypothesis based on group-average studies (52,58), future PFM would be required to define this functional location of the dlPFC in individuals to determine whether individualized functionally defined targets work better than standard anatomical targets (59,60).

PFM can uncover mechanisms that explicitly rely on differences in functional organization (Figure 3B). The discovery of heterogeneity in the size, shape, and layout in functional networks across individuals opens the possibility that some psychiatric illnesses may be associated with alterations in these features. Notably, alterations in, e.g., the size of a functional network would only be detectable in studies that describe these individualized features. Lynch *et al.* (48) provided a compelling example, obtaining PFM in patients with and without major depressive disorder. This work demonstrated that the surface area of the SN was 2 times larger in the individuals with major depressive disorder than healthy control participants. This SN expansion in patients with major depressive disorder was stable over time, independent of mood state, and primarily driven by border shifts between the SN and the DMN, frontoparietal network, and the cingulo-opercular network. Future work using PFM in other psychiatric illnesses is needed to test when other psychiatric disorders similarly associate with variation in brain organization.

PFM can detect mechanisms that vary across individuals with the same symptomatically defined disorder (Figure 3C). The mechanisms or circuit-level disruptions might vary across individuals with the same psychiatric disorder. Many different circuits have been implicated in anxiety disorders, for example, and one possibility is that the same apparent symptoms in different individuals result from differential dysfunction across these circuits. For example, increased activity in the ventral attention network in response to frightening stimuli may persistently direct attention to these stimuli in some children with anxiety, reinforcing their anxiety (61). In other children, decreased functioning of the frontoparietal network may decrease their ability to allocate executive function to modulate anxiety. Consistent with this framework, we recently demonstrated that the pattern of brain activity evoked by negative emotional stimuli is relatively consistent across healthy children, but the pattern is more variable across children with anxiety disorders, suggesting they each process negative stimuli in a more individual-specific manner (62).

PFM is uniquely poised to capture neural mechanisms that vary across individuals with the same symptomatically defined illnesses. One way to disentangle illness-causing versus benign individual brain differences is by using PFM in individuals while they are experiencing symptoms versus when they are not experiencing symptoms (i.e., measuring specific functional brain responses in the same individual in different states). In the study by Lynch *et al.* (48), for example, the RSFC of the SN differed when individuals were depressed versus not depressed. Furthermore, our group recently measured PFM in an individual woman with postpartum depression before and after treatment with brexanolone, a rapid-acting antidepressant (49). We detected widespread patterns of RSFC across individually defined functional brain areas that correlated with symptom severity over the course of treatment. This pattern may represent the RSFC signature of this person being in a depressed versus nondepressed state, although more work is needed with longer follow-up and more individuals to confirm this hypothesis. Notably, uncovering a reliable signature of an individualized mechanism could be useful in precision medicine applications. For example, PFM could be used to gauge whether an individual is responding to a specific treatment, if brain changes can be detected earlier in treatment course than changes in symptoms (63).

PFM AS A PROMISING TOOL TO STUDY THE ETIOLOGY OF PSYCHIATRIC ILLNESS ACROSS DEVELOPMENT

The altered neurodevelopmental trajectory of many psychiatric illnesses may begin near birth or earlier, making infancy an optimal window to uncover the developmental origins of psychopathology. Consistent with this model, prior studies demonstrate that regional brain volume (64), surface area (64), white matter metrics (65), and RSFC (9) as measured in the first weeks of life or even in utero (7,8) relate to psychiatric risk or later expression of symptoms. For example, variation in RSFC (10) and stimulus-evoked activity (66) of the ventral attention

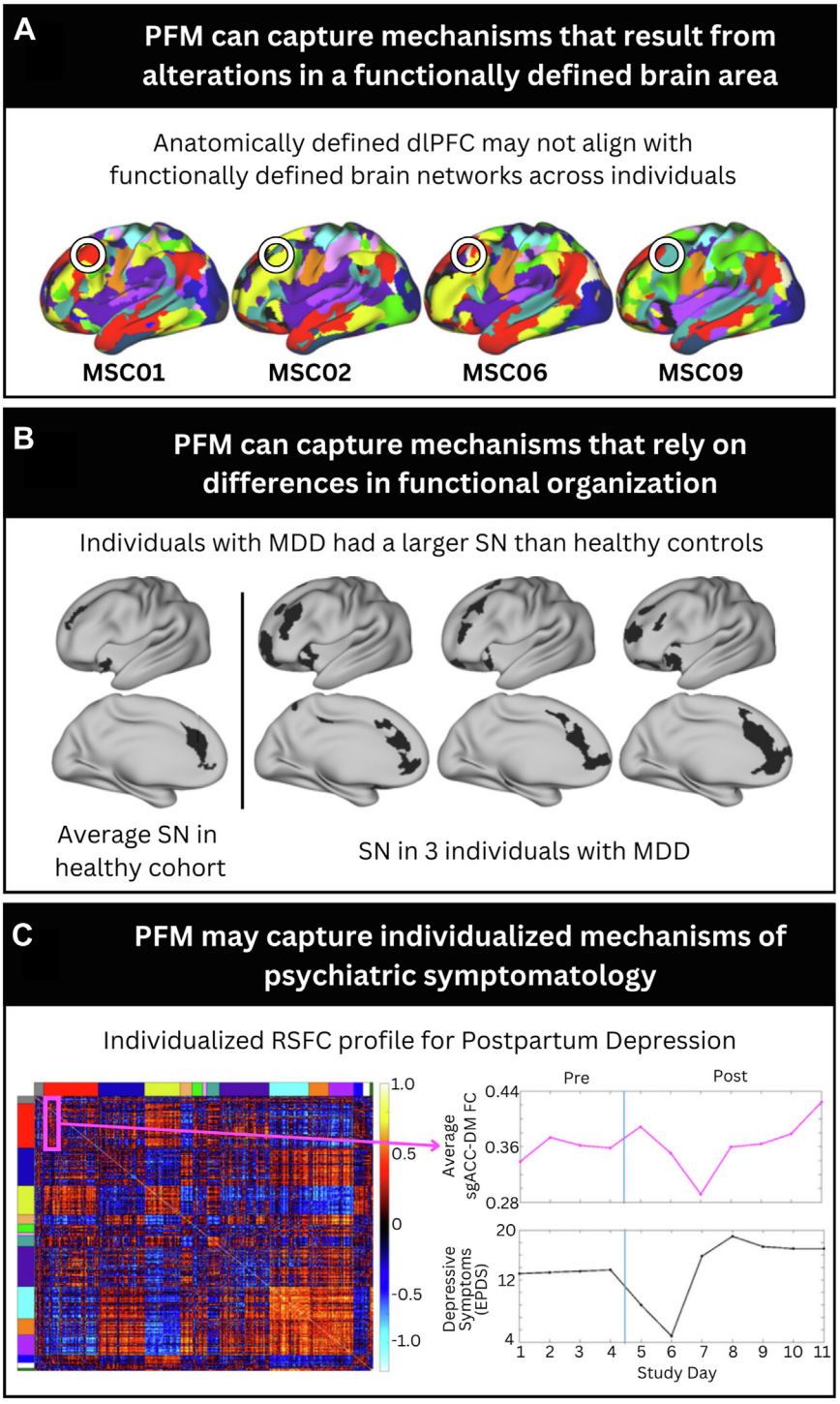

Figure 3. Novel applications of precision functional mapping (PFM) for psychiatric research among adolescent and adult populations. **(A)** PFM can characterize mechanisms of psychiatric illness that result from alterations in particular functionally defined brain areas by allowing for precise measurement of individual-specific functional brain areas and networks, rather than traditional anatomically defined areas. For instance, models of treatment-resistant depression posit altered activity in the subgenual anterior cingulate cortex (sgACC), potentially resulting from impaired regulation by the dorsolateral prefrontal cortex (dlPFC) (white circle), which has different functional definitions across individuals, as shown in this example. Thus, one hypothesis is that the efficacy of transcranial magnetic stimulation could be improved by stimulating the specific portion of the dlPFC with the highest magnitude of negative resting-state functional connectivity (RSFC) with the sgACC (i.e., defining transcranial magnetic stimulation targets based on functional definitions rather than anatomical definitions), given that functional definitions within the dlPFC vary across individuals. **(B)** PFM can uncover mechanisms that explicitly rely on differences in functional brain organization. In this example from Lynch *et al.*, work using PFM demonstrated that the surface area of the salience network (SN) was 2 times larger in the individuals with major depressive disorder (MDD) than healthy control participants. **(C)** PFM can detect mechanisms that vary across individuals with the same symptomatically defined disorder. In this example, we demonstrate an individual's specific pattern of RSFC that correlated with depression symptoms before and after treatment with brexanolone. Such patterns may vary across individuals, which can be detected with PFM. [Adapted from Figure 1A in Lynch *et al.* (48) **(B)** and Supplemental Figure 2 in Guard *et al.* (49) **(C)**, with permission]. DM, Default Mode Network; EPDS, Edinburgh Postnatal Depression Scale; FC, Functional Connectivity; MSC, Midnight Scan Club.

network in the neonatal period relates to risk of anxiety disorders later in life. While this work supports the hypothesis that the neurodevelopmental trajectories of some psychiatric illnesses may start near birth, we are still lacking coherent neurodevelopment models that characterize how these early variations unfold over development resulting in symptoms later in childhood and adulthood. Many specific mechanisms have been proposed, including 1) alterations in the developmental timing of the maturation of specific circuits, 2) cascading influences in which such early alterations cause or are amplified

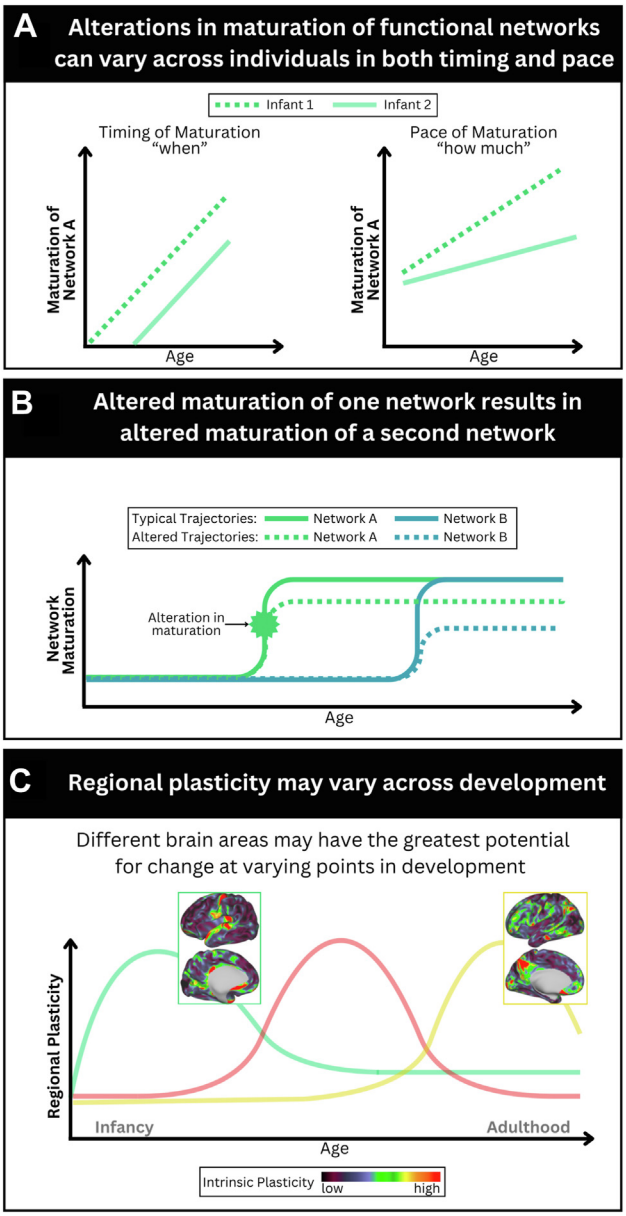

Figure 4. Precision functional mapping (PFM) affords the unique opportunity to test common theories of neurodevelopmental mechanisms of psychiatric disorders. **(A)** Psychiatric illness may arise due to alterations in the timing of maturation of relevant neural circuits. This example illustrates the maturational trajectory of network A in 2 individuals and how alterations in the typical maturational trajectory can either be in the timing of maturation of network A (when is the change) or the maturational pace (how much change is there). PFM can be useful in characterizing whether alterations in the timing of maturation or the maturational pace of specific neural measures, such as network functional connectivity, relate to expression of psychiatric symptoms. **(B)** Psychiatric illnesses may emerge as a result of altered neurodevelopmental cascades, in which early neural alterations cause a cascade of altered neurodevelopment later in life. In this example, network A (green) is a typically early maturing network and network B (blue) typically matures later, relying on environmental inputs encoded by network A. Thus, in this example, when network A has an altered maturational trajectory in an infant such that it does not reach its peak maturation level when it is intended to, environmental inputs are improperly encoded, resulting in downstream effects to network B's maturational trajectory. **(C)** Psychiatric illnesses may be associated with overall changes in neural plasticity that can influence adaptation of neural circuits to the environment. In this example, we depict that regional plasticity (i.e., measures of plasticity in different brain networks or regions) may vary across development, whereby peaks in plasticity for various brain regions occur at different points in development. PFM can allow for investigations of plasticity and track plasticity of specific brain regions across development to identify when they may be most susceptible to interventions.

by later alterations, and 3) alterations in neural plasticity and developmental epochs in which interventions (either natural or experimental) have a large impact on brain function. While there is some support for each of these theoretical models, our current work is hampered by an impoverished understanding of these mechanisms in both typical and atypical brain development. Thus, in this section, we highlight specific ways in which PFM may be useful for characterizing these specific mechanisms and testing models of psychiatric illnesses that are inherently developmental in nature.

PFM Can Be Used to Characterize Normative Neurodevelopment

Infancy is a developmental period marked by striking growth throughout the brain that serves as a starting point for postnatal experience–dependent learning (67,68). The brain doubles in size across the first year and continues to grow until it reaches approximately 90% of its adult size at age 6 to 8 years (69). Growth of specific brain systems is nonlinear; for instance, the striatum and thalamus peak in growth at approximately ages 3 to 5 years (68,70) while white matter continues to expand well into late childhood (71,72). Rapid and complex structural and functional development (73) is determined by a combination of genetics and experience-dependent plasticity, both of which may constitute psychiatric risk factors. As a result, infancy is likely a period of particularly individual-specific neurodevelopment. Indeed, in recent work, we were unable to define a set of cortical areas that reliably cover the whole brain at the group level in infants due to extensive heterogeneity in area boundaries; however, such a reliable parcellation of the entire cortical surface is possible in an individual infant using PFM (74). This, along with other work in infants (75,76) as well as children and adolescents (77) suggests that individuals vary in developmental trajectories of cortical areas and functional brain networks. Therefore, PFM is important for describing normative brain development, reducing challenges related to heterogeneity in the location and pace of functional brain area and network development.

PFM Could Uncover Developmental Mechanisms of Psychiatric Illnesses

PFM affords the unique opportunity to uncover novel mechanisms of psychiatric disorders and to test common theories of neurodevelopmental mechanisms of psychiatric disorders, including theories relating to 1) altered neurodevelopmental timing, 2) altered neurodevelopmental cascades, and 3) alterations in plasticity.

Work suggests that some psychiatric illnesses may result from alterations in the timing of specific circuit maturation of an

individual child relative to their peers (Figure 4A). For example, psychosocial neglect in infancy and early childhood can change the pace and timing of maturation of regulatory circuitry (78), which may result in a psychiatric disorder later in life. Consistent with this framework, in a large longitudinal randomized controlled trial of institutionalized children, children who were left in foster care (institutionalization) had slower rates of cortical thinning in brain regions involved in social processing across ages 9 to 15 years relative to children who were adopted (79). The institutionalized children also had significantly elevated risk of psychopathology (80). Given that it is not ethical or feasible to conduct a randomized controlled trial in children to study all candidate environmental variables that could alter neurodevelopmental trajectories, PFM is one of the few techniques that can give precise insight to an individual's neurodevelopment to test theories of altered neurodevelopment leading to psychiatric disorders. Alterations in developmental timing can be studied by repeating PFM across development alongside careful measure of the child's individual experiences, behaviors, and abilities. As such, PFM can be used to characterize whether alterations in the timing of maturation of brain networks and circuits (when is the change) or the maturational pace (how much change is there) of specific neural measures, such as network functional connectivity, relate to expression of psychiatric symptoms.

Additional theories posit that psychiatric illnesses may emerge following altered neurodevelopmental cascades, in which early neural alterations cause a cascade of altered neurodevelopment later in life (Figure 4B). Subsequently developing circuits mature differently in response to earlier neural alterations. Alternatively, subsequent alterations may amplify the functional consequences of earlier alterations. For example, alterations in infant brain networks responsible for sensory or stimulus-drive attention may alter how the infant interacts with their environment, such as finding ambiguous social stimuli to be overstimulating and therefore distressing. This early alteration could therefore have a cascading effect, resulting in different neural input to higher-order and later developing brain networks such as those involved in goal-directed attention and self-regulation, influencing how the child's brain processes and interprets ambiguous social stimuli (81). This consistently altered input could skew the development of these higher-order networks, resulting in a psychiatric illness such as social anxiety disorder. Because experiences are highly individual specific, PFM is among the only tools uniquely able to track the development of these different brain networks in individuals and test theories of cascading influences of individual differences in infant neurodevelopment.

Other work suggests that some psychiatric illnesses are associated with overall changes in neural plasticity—the potential for a given circuit to change—which can influence adaptation of neural circuits to the environment (Figure 4C). Research conducted in animal models suggests that neural plasticity is influenced by a range of genetic (experience-independent), experience-expectant, and experience-dependent processes that influence the ability of a given neuronal population to adapt in structure or function over time (82–85). For instance, by not providing a child with the developmentally expected level of caregiver interactions in early childhood—the period when children are making the greatest gains in developing emotion identification, social, and self-regulation skills (86–88)—they may miss receiving necessary inputs during a sensitive period of socioemotional development and alter the developmental trajectory of the associated brain circuits. Although preliminary, emerging evidence indicates that fMRI can be used to measure plasticity, either by collecting data before and after an intervention and noting the degree of change in response to the intervention or through the use of candidate markers of plasticity such as the amplitude of low frequency fluctuations (25). As neuroimaging to measure plasticity improves (89), PFM used in combination with targeted intervention and appropriate controls will be able to provide evidence for or against specific theories of plasticity across development. Similarly, sensitive periods are characterized by periods of heightened plasticity (90), and incorrect inputs during these periods of increased plasticity, such as early-life psychosocial stress, may confer lasting changes to affected circuitry. Thus, PFM could be used to explicitly test theories that psychiatric illnesses emerge as a result of altered developmental plasticity or incorrect inputs during periods of high plasticity (91).

While many of these theoretical developmental mechanisms of psychiatric illness have yet to be empirically supported, PFM provides the tools necessary to precisely characterize normative and altered neurodevelopment. We suggest that future PFM work 1) track the developmental trajectory of brain systems of interest for psychiatric illness; 2) track the developmental trajectories of these systems in infants at high risk of psychopathology, perhaps focusing on the mechanisms highlighted above; and 3) test whether low-risk interventions (i.e., socialization, exposure to novelty, executive function/attention training) can influence neurodevelopmental trajectories and reduce psychiatric risk.

Limitations of PFM in Early Development

The benefits of PFM should be considered in light of its limitations. While our group has successfully collected 2+ hours of low-motion fMRI data in several infants over the course of days (74,92,93), routinely collecting sufficient data for PFM in developmental samples may be practically difficult. Future work should explore technological and methodological advances that may improve reliability without requiring longer scan times, such as multiecho sequences (93–95) and denoising algorithms (96,97). Infant fMRI data are usually collected during natural sleep (98–100), and future work is required to determine how functional brain responses and functional connectivity metrics vary with sleep stage (101). In addition, work in adults indicates that depending on study goals, there may be an optimal balance between how much data to collect in an individual and how many participants to enroll in a particular study (102). An important goal of future work using PFM in developmental samples is to similarly determine the right balance among 1) amount of data in a single individual, 2) the number of longitudinal follow-ups, and 3) the number of individuals to include in a study. Finally, currently there is no consensus in the scientific community regarding the number, nomenclature, and distribution of functional brain systems present in humans, and this challenge is compounded in PFM in that individuals may show features

of systems that are not present in group-average characterizations. Thus, careful consideration has to be taken in PFM in terms of how to define and label brain systems.

CONCLUSIONS

PFM represents a groundbreaking approach in psychiatric research, enabling detailed exploration of individual-level brain organization over the course of the life span. While its applications in adult and adolescent populations have yielded significant insights, extending PFM to infancy and early childhood remains an unexplored territory with immense potential. Establishing connections between individual variations in functional brain organization during development and the emergence of psychopathology will pave the way for identifying diagnostic and treatment markers. The ability of PFM to bridge the gap between individual differences in brain function and psychiatric symptomatology and treatment outcomes provides a promising avenue for advancing personalized interventions and prevention.

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