Precision functional magnetic resonance imaging reveals individualized brain functional network organization postprint

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Abstract

Precision functional magnetic resonance imaging (pfMRI) refers to a data acquisition strategy that collects extensive fMRI data from individual subjects. In contrast to traditional fMRI studies that acquire limited data per subject and subsequently reveal brain functional patterns underlying cognitive processes or shared functional characteristics across specific populations through group averaging, this method' s advantage lies in its capacity to uncover individual-specific brain features. Consequently, it has garnered increasing attention and adoption among researchers. To date, numerous studies have utilized this approach to systematically elucidate individualized brain functional network organization from six perspectives: inter-individual variability in functional network organization, individual identification, functional localization of regional areas, identification of individual network hubs, development and plasticity of individual functional networks, and clinical applications. These research findings hold significant implications for future brain science research. Future research should prioritize investigating the relationship between the characteristics of individual functional network organization revealed by existing studies and behavioral performance, reducing the requisite scanning time for this method through advancements in data analysis and imaging techniques, and endeavoring to apply this methodology to task-based fMRI and multimodal data integration studies.

Full Text

Precision Functional Magnetic Resonance Imaging Reveals Individualized Brain Functional Network Organization

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Abstract: Precision functional magnetic resonance imaging (pfMRI) refers to a data acquisition strategy that collects large amounts of fMRI data from single individuals. Compared with traditional fMRI research, which typically collects a small amount of data from each participant and then reveals the underlying brain mechanisms of cognitive processes or the shared brain functional features of a specific population through group averaging, the advantage of this method is that it can reveal the brain characteristics of each individual. Consequently, it has increasingly attracted researchers'attention and application. To date, numerous studies have employed this method to systematically reveal individualized brain functional network organization from six perspectives: individual differences in functional network organization, individual identification, functional localization of local regions, identification of individual network hubs, development and plasticity of individual functional networks, and clinical applications. These research findings provide important insights for future brain science research. Future studies should focus on exploring the relationship between the characteristics of individual functional networks and behavioral performance, reducing the scanning time required by this method through improvements in data analysis and imaging technology, and attempting to apply this method to task-state fMRI and multimodal data fusion research.

Keywords: precision functional magnetic resonance imaging, brain functional network, individual difference, functional connectivity

Classification Number: B845

Since Kwong et al. and Ogawa et al. used functional magnetic resonance imaging (fMRI) to explore human brain function in 1992 (Kwong et al., 1992; Ogawa et al., 1992), fMRI has gradually become an important tool for understanding human brain function, yielding numerous research findings in cognitive neuroscience, psychology, and medicine that reveal the neural basis of processes ranging from basic sensation to complex cognition. One significant achievement has been the description of human brain functional network organization based on resting-state functional connectivity (RSFC), such as the default mode network (DMN) and frontoparietal network (FPN). Brain regions belonging to the same functional network may be spatially separated but exhibit highly correlated activity patterns over time (Doucet et al., 2011; Power et al., 2011; Yeo et al., 2011). Moreover, several common psychiatric disorders are closely related to dysfunction in these distributed brain networks, including depression, schizophrenia, and Alzheimer' s disease (Barch, 2017; Karbasforoushan & Woodward, 2012; Mayberg, 2007; Sha et al., 2019). Surprisingly, however, the translation of these basic research findings into clinical applications has often proven difficult. One major reason is that previous studies mostly adopted group-average research designs. While this approach is important for revealing general principles of brain

functional organization, it has considerable limitations in capturing individual characteristics.

The primary reason why previous studies mostly used group-average designs is that the BOLD signal itself contains noise from multiple sources, such as thermal motion of free electrons in the system, physiological (respiration, motion) and non-physiological noise, making it difficult to obtain reliable results from individual fMRI data with standard scan lengths (5–10 minutes) (Liu, 2016). However, from a psychometric perspective, random error variance has more opportunities to cancel itself out with larger data quantities, thereby increasing the proportion of true score in the measurement and improving test reliability (Elliott et al., 2021). Therefore, some researchers have recently attempted to investigate the characteristics of individualized functional network organization by increasing individual fMRI scan length, an approach termed precision functional magnetic resonance imaging. Gratton, Kraus et al. (2020) summarized early research findings using the pfMRI method and proposed that this approach shows good prospects for promoting the practical translation of research findings and clinical applications, such as identifying individual-specific targets for transcranial magnetic stimulation (TMS), understanding differences between normal and pathological brains that are masked in group-level studies, long-term tracking of treatment effects, and providing biomarkers to identify high-risk individuals. However, that article was completed in the early stages of pfMRI method development, when research findings were limited (only covering individual differences and network variation in functional network organization) and its main purpose was to illustrate the promising prospects and development directions of this method in mental disease treatment. In recent years, numerous studies have employed the pfMRI method to reveal individualized functional network organization from different research perspectives, yielding rich research findings. Currently, there is a lack of systematic review and summary of these achievements. Here, based on relevant literature from 2020 and later (accounting for 71.7% of the total pfMRI literature), this article systematically reviews research findings using the pfMRI method to reveal individual differences in functional network organization, individual identification, functional localization of local regions, identification of individual network hubs, development and plasticity of individual functional networks, and their clinical applications. It summarizes the advantages and limitations of existing research and proposes directions for further exploration, providing important support for future basic research and practical applications in brain science.

2 Introduction to pfMRI

pfMRI is essentially a data acquisition strategy that involves long-duration fMRI scanning of single subjects to provide sufficient high-quality data for mapping individual brain function. Additionally, some classic pfMRI datasets typically include multimodal data. For example, the MyConnectome dataset includes structural images (T1-weighted, T2-weighted, and diffusion tensor imaging (DTI)),

functional images (task-state and resting-state), gene expression, and metabolic indicators collected from a single subject over an 18-month time span (Poldrack et al., 2015). The Midnight Scan Club (MSC) dataset includes structural images (T1-weighted, T2-weighted, magnetic resonance angiogram (MRA), magnetic resonance venogram (MRV)), functional images (resting-state and task-state), and a set of neuropsychological tests (involving intelligence, personality, etc.) from 10 subjects (Gordon et al., 2017). It should be noted that although these datasets include data from multiple modalities, most existing pfMRI studies have only used resting-state data to reveal individual functional network characteristics. In these studies, resting-state fMRI scanning times ranged between 0.4 and 32 hours, with data quantities ranging from 565 to 79,360 time points, which are significantly higher than traditional fMRI studies (typically 5–10 minutes). Simultaneously, to further improve data quality and ensure stability of individual results, pfMRI research has implemented relatively strict control of head motion noise. For example, in the preprocessing of most pfMRI studies, images with framewise displacement (FD) greater than 0.2 mm were removed (Dworetsky, Seitzman, Adeyemo, Neta, et al., 2021; Faskowitz et al., 2020; Gordon et al., 2017; Lynch et al., 2019; Perez et al., 2023), whereas traditional fMRI studies either did not use this method for further head motion control or used more lenient thresholds (generally removing images with FD $>$ 0.5 mm) (Duda et al., 2021; Fan et al., 2021; Power et al., 2012; Sripada et al., 2020; Tarchi et al., 2022). In summary, compared with traditional fMRI methods, pfMRI imposes higher requirements on both data quantity and quality.

However, it should be noted that several hours of data collection is not necessarily required by the pfMRI method. The lengthy scanning time in early pfMRI research may have been due to its exploratory nature—researchers were uncertain how long scanning time would be needed to obtain stable and reliable individualized results, so they increased scan length as much as possible. Therefore, some researchers have investigated the relationship between fMRI data quantity and stability of individual results. The typical approach is to divide fMRI data from the same individual into two parts and use the correlation between result metrics obtained from the two parts as an indicator of stability (higher correlation indicates greater stability), then observe how result stability changes with data quantity. Laumann et al. (2015) first investigated the stability of cortical functional connectivity matrices, finding that at least 40 minutes of low-motion data were needed to obtain relatively stable individual results ($r > 0.9$). Gordon et al. (2017) further investigated the stability of other measurement metrics, finding that the modularity coefficient required only 10 minutes of data, network assignment and global efficiency required 90 minutes, but even 100 minutes of data did not stabilize the participation coefficient ($r < 0.65$). Other studies further found that the stability of functional connectivity in different cortical regions also varied. For example, using 30 minutes of data, only 28% of brain regions showed reliability higher than 0.7 (Lynch et al., 2020). Compared with the cerebral cortex, some studies found that functional connectivity stability in subcortical structures is generally lower, thus

requiring more data. For example, Marek et al. (2018) found that 90 minutes of data were needed to achieve high reliability in cerebellar functional connectivity; for the basal ganglia and thalamus, 100 minutes of data were required (Greene et al., 2020). This higher data requirement may be related to lower signal-to-noise ratios in these regions. Additionally, Raut et al. (2020) found that compared with functional connectivity patterns, the stability of temporal lag structure (the temporal progression of activity in different brain regions) was worse, requiring more than 100 minutes of data to obtain stable individual results. Beyond the scan lengths examined in the above studies, research has also shown that increasing the number of scanning sessions can improve the reliability of functional connectivity when scan length is fixed (Bergmann et al., 2020; Noble et al., 2017). Therefore, repeated-measurement fMRI designs are highly advantageous for identifying individualized functional connectivity patterns. In summary, these results demonstrate that the data quantity requirements of pfMRI methods vary considerably across different brain regions, outcome metrics, and scanning sessions.

3 Individualized Functional Network Organization

3.1 Individual Differences in Functional Network Organization Poldrack et al. (2015) first conducted long-term longitudinal fMRI scanning of a single subject, collecting multimodal data from the author Poldrack himself over an 18-month period. This study not only revealed the stability and specificity of individual functional network organization but also demonstrated that such individualized features have biological significance (correlating with metabolic and genetic indicators), leading many researchers to focus on this field and conduct in-depth investigations. Initially, researchers' main focus was on using pfMRI methods to explore individual cortical functional network organization features. Laumann et al. (2015) first attempted to perform individualized areal parcellation of the cerebral cortex using pfMRI methods, finding that individual-based parcellation was significantly superior to group-average parcellation (based on existing datasets from 120 subjects, Gordon et al., 2016; Wig et al., 2014) and the AAL template, and showed high consistency with task activation (task activation boundaries were similar to individualized parcellation). Meanwhile, substantial functional network variation was observed between individuals, primarily concentrated in association networks (such as FPN, DMN, cingulo-opercular network (CO), and attentional network). To promote development in this emerging research field, Gordon et al. (2017) collected pfMRI data from 10 subjects (the MSC dataset). This study revealed individual differences in functional network organization and further found that cortical myelin content corresponded to individual differences in functional network topology. Beyond the human brain, Bergmann et al. (2020) found that functional connectivity in mice also exhibited individual uniqueness, and that mice could be successfully identified through functional connectivity matrices. However, unlike the human brain, individual effects in mouse cortical functional network organization showed no difference between sensory and association systems, whereas inter-individual

variation in the human brain is mainly concentrated in association systems. Additionally, Ren et al. (2021) investigated and compared individual variation in the auditory cortex of humans and macaques, finding that individual variation in the auditory cortex was significantly greater than in the visual cortex, and that low-variation regions in the auditory cortex showed stronger functional connectivity with sensorimotor cortex, while high-variation regions showed stronger functional connectivity with frontal poles. This suggests that low-variation regions in the auditory cortex may be involved in primary information processing, while high-variation regions may be involved in higher-order association processing in the frontal lobe. Not limited to functional connectivity patterns, research has also revealed inter-individual differences in temporal lag structure. However, as mentioned earlier, the stability of temporal lag structure is worse than that of individual functional connectivity patterns, requiring larger data quantities to obtain stable individual results (Raut et al., 2020).

It should be noted that all the studies described above were based on traditional functional connectivity (also called nodal functional connectivity, nFC), which uses nodes as the basic units of brain structure and function, calculating the correlation between activity in two nodes. A major limitation of this method is that it cannot capture potential relationships between network edges that may have meaningful implications. However, analysis of edge interactions in other scientific fields has provided important perspectives for understanding the organization and function of complex systems (Ahn et al., 2010; Evans & Lambiotte, 2009). Based on this, Faskowitz et al. (2020) proposed a framework for studying individual brain functional networks based on functional connectivity edges, where the temporal unfolding of correlations between brain activity in two regions is called an "edge," and the correlation between two "edges" is called edge functional connectivity (eFC). This study used pfMRI methods to confirm that eFC can also capture individual features, and that linear combinations of nFC are not similar to eFC, indicating that the two methods reveal unique organizational features of the nervous system and should be considered complementary approaches. Additionally, the study found unique advantages of eFC compared with nFC, such as being less constrained by brain topography and revealing overlapping network structures in the cerebral cortex (i.e., assigning one node to different networks, which is difficult to achieve with nFC). Esfahlani et al. (2021) replicated the results of Faskowitz et al. (2020) and further explored overlapping communities based on eFC at the system level. The results showed that overlapping networks constructed based on eFC also exhibited subject specificity, with variation concentrated in control networks, temporoparietal regions, and dorsal attention networks, consistent with results from nFC. The researchers emphasized that the discovery of overlapping networks is important for revealing brain function, and that such functional overlap may be a key principle of brain network organization.

Based on the above research, it can be found that functional network organization in both cerebral cortex and subcortical structures exhibits inter-individual variability. On this basis, some researchers have shifted their perspective to

investigate characteristics of regions where individual and group-average functional connectivity patterns differ, referring to these regions as "network variants." Seitzman et al. (2019) first proposed this concept and found that network variants could be observed in all individuals, but the location, size, and functional network membership of the variants differed between subjects. However, network variants also showed commonalities across subjects, frequently appearing in association networks, and the functional connectivity patterns at variant locations corresponded to their network identity, consistent with findings from the previous section. Building on previous research findings on network variants, Dworetsky, Seitzman, Adeyemo, Neta et al. (2021) attempted to construct probabilistic brain network maps using pfMRI datasets (i.e., the proportion of subjects in which a given voxel is identified as belonging to a particular network. For example, if 20 out of 100 subjects are identified as default network and 80 as salience network, the corresponding proportions are 20% and 80%). Through these maps, they found that all 14 classic networks contained regions with high inter-group consistency, but also regions with low inter-group consistency. These results were successfully replicated across multiple datasets. Importantly, based on the 264 ROIs proposed by Power et al. (2011), the study identified 153 ROIs with high inter-group consistency and created a point-and-click tool through which the specific coordinates of the 153 ROIs and the network probability corresponding to each voxel in the cortex can be queried.

In summary, the studies in this section have revealed individual functional network organization and demonstrated its inter-individual variability from different brain regions (cerebral cortex and subcortical structures) and different data analysis perspectives (nFC and eFC). These inter-individual functional network variations mainly appear in association networks and remain stable across different states. The findings in this section demonstrate the unique advantages of pfMRI methods over group-average fMRI methods, namely the ability to stably reveal individual brain characteristics. On the other hand, these results also suggest that individual differences, which are often ignored in previous group-average research designs, are likely to confound final research results. Therefore, researchers need to consider this issue in study design or result interpretation. Some researchers have already proposed feasible solutions to this problem, as detailed in the "network variants" section below.

3.2 Individual and State Identification Based on Individual Functional Network Organization Differences The research findings described in Section 3.1 collectively demonstrate that functional network organization has individual specificity. Therefore, some researchers have attempted to use these features for individual identification and have achieved certain results. For example, Wang et al. (2021) found that individual functional connectivity patterns could successfully identify newborns, with accuracy reaching up to 100%. The brain regions making major contributions were mainly located in higher-order brain systems (such as medial and lateral frontal cortex, superior parietal gyrus, anterior and middle cingulate cortex, and left inferior temporal gyrus). Differ-

ent from this study, Yang et al. (2022) revealed that brain coactivation patterns (CAPs, the dynamic changes in brain functional connectivity over time) could also produce good individual identification results, characterized by low inter-individual similarity and high intra-individual similarity. Additionally, Jo, Faskowitz et al. (2021) found that when sufficient data were available (approximately 30 minutes), subject identification performance based on eFC was even better than that based on nFC. However, consistent with nFC, higher-level cognitive systems (such as control networks, attention networks, and DMN) played major roles in eFC-based individual identification, supporting the conclusion that inter-individual variation in functional networks mainly occurs in association networks.

Beyond individual identification, some researchers have found that functional organization also differs between task states (Salehi et al., 2020). Therefore, Porter et al. (2023) attempted to identify task states through cortical functional connectivity matrices, finding that classifiers trained on the same subject showed higher identification rates for task states than those trained on different subjects. This result not only supports differences in brain functional organization between different task states but also indicates the individual specificity of task states, i.e., individualized brain organization exists not only in resting state but also universally in functional organization during task states. In summary, research in this section further supports individual differences in functional network organization from the perspective of individual identification and demonstrates that such individual differences are trait-like, laying a foundation for future investigations of their relationship with stable behavioral characteristics.

3.3 Functional Localization of Individual Default Mode Network Subnetworks and Inferior Frontal Gyrus Since the proposal of the pfMRI method, some researchers have attempted to use it for functional localization of local brain regions, with current research focusing mainly on the DMN. The key reason is that some researchers believe the DMN may contain functionally distinct subnetworks (Andrews-Hanna et al., 2010, 2014; Leech et al., 2011), and group-average data may obscure the details of this division, making it unsuitable for precise description of DMN subnetworks. Therefore, some researchers have attempted to explore the organizational details of the DMN from an individual perspective. Braga and Buckner (2017) first identified two DMN subnetworks (Network A and Network B) in four subjects. These two subnetworks not only showed different functional connectivity patterns but also exhibited large individual differences in their division. Based on this research, Braga et al. (2019) further used 7T fMRI (with higher resolution) to investigate the distribution of the two DMN subnetworks in individuals, finding that the two subnetworks were closely juxtaposed and interdigitated, validating and supplementing previous results. DiNicola et al. (2020) found that Networks A and B showed different task activation patterns: all subjects showed higher activation in Network A during contextual prediction tasks, while all subjects showed higher activation in Network B during theory-of-mind tasks, further demonstrating the functional

segregation of the two DMN subnetworks. Gordon et al. (2020) performed a more detailed parcellation of the DMN, finding that the DMN of all 10 subjects could be divided into 9 subnetworks, with the parietal subnetwork serving as the center of the DMN, connecting to other subnetworks. These networks showed good correspondence with task activation, again supporting functional segregation within different DMN regions. Additionally, some researchers have investigated inter-individual variation in connectivity between the DMN and other networks (FPN), finding that the strongest connections (typically 10-20 connections, usually within-network connections) did not show inter-subject variation, while inter-individual variation mainly appeared in connections between the two networks (Oliver et al., 2019).

In addition to DMN-related research, Suda et al. (2020) used pfMRI methods to parcellate subregions of the inferior frontal cortex (IFC), finding that the IFC could be divided into 6 regions, including ventral posterior IFC, dorsal posterior IFC, inferior frontal junction, middle IFC, ventral precentral sulcus, and dorsal precentral sulcus. In both group-level and individual-level analyses, response inhibition in the stop-signal paradigm was associated with lower-level brain activation in the middle IFC module. Overall, these research results demonstrate the fine-grained nature of brain functional parcellation, with different regions within the same system potentially responsible for different functions. Meanwhile, the pfMRI method can be used not only to explore the specificity of individual functional organization but also shows great potential for fine functional localization of the brain.

3.4 Identification of Individual Network Hubs Network hubs refer to nodes with high functional connectivity to other regions, typically connecting to multiple brain areas and occupying central positions in networks. Researchers generally believe these hubs play important roles in information flow transmission and integration (Sporns, 2013; Tomasi & Volkow, 2011; van den Heuvel & Sporns, 2013). Previous research on network hubs also generally used group-average methods (Bertolero et al., 2015; Power et al., 2013). However, network hubs revealed through this method have an alternative explanation: the connectivity patterns shown by network hubs may be caused by individual differences in functional networks between subjects and may not truly exist (Gordon et al., 2017; Gordon, Lynch, et al., 2018; Smith et al., 2023). Therefore, some researchers have attempted to use pfMRI methods to reveal individual brain network hubs to overcome the limitations of traditional group-average methods and further support the concept of network hubs. Gordon, Lynch et al. (2018) first successfully identified individual network hubs based on participation coefficients, supporting the existence of network hubs in individuals. Furthermore, this study classified the identified hubs into three categories through cluster analysis: control-default connector hubs, cross-control connector hubs, and control-processing connector hubs. These three types of hubs showed different connectivity patterns, and damage to different types of hubs had separable effects on brain network organization. Smith et al. (2023) compared group-average

identified hubs with network variant locations, finding that group network hubs identified based on participation coefficients had little overlap with network variants, and that hub connectivity patterns were relatively consistent across subjects. These results all prove that network hubs truly exist in functional networks and are not derived from inter-individual variability in functional networks, further supporting and supplementing findings on network hubs from group-average research. Lynch et al. (2019) located hubs in individual right middle frontal gyrus and inhibited hub location activity using continuous theta burst stimulation (cTBS) to observe its effects on task performance. The study found that the spatial distribution of individual hubs was not consistent, nor was it consistent with group-average hub distribution. When cTBS was used to inhibit hub activity, it interfered with task performance, mainly due to inhibition of control-processing connector hub activity proposed by Gordon, Lynch et al. (2018). Overall, research findings in this section demonstrate that the pfMRI method overcomes the limitations of traditional fMRI research in revealing brain network hubs, further supporting the concept of "network hubs" proposed in previous research, and shows that network hubs also exhibit variability between individuals.

3.5 Research on Development and Plasticity of Individual Functional Networks Most of the research findings described above used adults as subjects, with few studies investigating how brain functional organization and its inter-individual variation develop continuously with age. To address this issue, Cui et al. (2020) used high-quality fMRI data from 693 subjects (aged 8–23 years) with 27-minute scan lengths to investigate the developmental aspects of functional networks. The study found that network variants were similar across different age groups, and these variant locations typically had unique characteristics, such as high blood flow and evolutionary expansion, and low cortical myelin content. However, there were also differences in functional network topography, such as cortical representations of motor and visual networks decreasing significantly with age. Additionally, complex patterns of network topography could highly accurately predict age, with association networks playing the most important role in age prediction. Regarding plasticity of brain functional organization, Pritschet et al. (2020) investigated the relationship between hormone levels throughout the menstrual cycle and functional networks in women, finding that brain connectivity increased with serum estradiol, mainly manifested in temporoparietal networks. Moreover, estradiol content over two days could predict functional connectivity. At the same time, there was a certain relationship between estradiol and functional network topography, manifested as estradiol content being related to participation coefficients or global efficiency of some networks (such as DMN, DAN, control networks, and temporoparietal networks). Newbold et al. (2020) explored plasticity of brain functional organization using limb constraint (right hand) methods. The study found that limb constraint caused obvious behavioral changes, with significant reductions in usage rate, grip strength, and fine motor skills of the constrained limb. In terms of brain

functional organization, the upper extremity region in left somatomotor cortex (L-SM1ue) showed obvious disconnection from other motor areas, and spontaneous activity pulses appeared in the corresponding upper extremity subcircuit (L-SM1ue, left supplementary motor area, and right cerebellum). Newbold et al. (2021) further explored the mechanism of plasticity on the basis of replicating previous results, finding that changes in brain functional networks during limb constraint mainly manifested as increased connectivity between L-SM1ue and the cingulo-opercular network (CON), and decreased connectivity with other somatomotor cortex regions. The increased connectivity was mainly due to the appearance of spontaneous activity pulses (spontaneous activity pulses between CON and L-SM1ue may be related to normal maintenance of disused neural circuits and preparation for functional recovery), which helps protect neural circuits from functional degradation caused by limb constraint, while decreased connectivity with other somatomotor cortex regions may be due to Hebbian-like disconnection.

To date, research using pfMRI methods on development and plasticity of individual functional networks has made preliminary progress, revealing the maturation process of individual brain functional network organization and how it is influenced by hormonal and environmental factors. However, current research still has certain limitations that need to be addressed in future studies. For example, in terms of individual functional network development, the 27-minute fMRI data used by Cui et al. (2020) is still insufficient. Based on previous introductions, at least 40 minutes of high-quality data are needed to obtain stable individualized results. Moreover, the age span included in this study is insufficient, failing to cover functional network changes in infancy, middle age, and old age. Therefore, an important direction for future developmental research should be to collect more high-quality fMRI data for individual subjects while considering increasing the age span of developmental studies to accurately depict how brain functional networks develop and change throughout the human lifespan. In terms of plasticity of individual functional networks, current research mainly focuses on the effects of behavioral manipulations or menstrual cycles on functional networks in normal individuals, but few studies have examined changes in functional networks in patients with neurological diseases and improvements in their functional networks through various treatment methods. Research in this area is important for the prevention, diagnosis, treatment, and tracking and evaluation of treatment effects of neurological diseases.

3.6 Clinical Application Research Since the proposal of the pfMRI method, some researchers have believed it may have great potential in clinical applications, prompting some researchers to conduct preliminary studies in this area. One major direction is the localization of individualized stimulation targets in TMS treatment. Previous research found that TMS treatment for depression symptoms is more effective when stimulating dorsolateral prefrontal cortex (DLPFC) regions that show stronger negative correlation with the subgenual cingulate cortex (SGC) (Fox et al., 2012). Cash, Cocchi, Lv, Wu et

al. (2021) first demonstrated that individualized stimulation targets identified through pfMRI methods all showed negative functional connectivity with SGC, and target locations were relatively stable within one year, though they differed between individuals. However, a clear limitation of this method is the need for more fMRI data (over 20 minutes). At the same time, Cash, Cocchi, Lv, and Zalesky (2021) did not use pfMRI data, but they found that individualized targets obtained through 13 minutes of fMRI data could significantly improve treatment effects, manifested as a significant negative correlation between the distance from actual stimulation targets to individualized targets and treatment effects, while the distance between actual stimulation targets and group-average targets showed no significant correlation with treatment effects. Combined with Cash, Cocchi, Lv, Wu et al. (2021) using pfMRI methods for stable localization of individualized stimulation targets, these two studies together demonstrate that this method has considerable potential for improving TMS treatment effects. Sun et al. (2022) investigated the minimal scanning time required for individualized stimulation targets (superior to those determined by group-average data). First, for negative DLPFC-SGC connectivity, both healthy subjects and depression patients required more than 40 minutes of fMRI data to obtain individualized targets superior to group-average targets. Second, for positive connectivity between the inferior parietal lobule (IPL) and hippocampus, at least 8 minutes of data were needed to obtain individualized targets superior to group-average targets. These results indicate that different regions require different data quantities for determining individualized stimulation targets, which may be related to previously mentioned differences in inter-individual variability across functional networks. Lynch et al. (2022) proposed a new method for determining individualized TMS stimulation targets based on previous research: targeted functional network stimulation (TANS). This study demonstrated in both simulated and real-world scenarios that compared with traditional methods (determining stimulation location based on the same MNI coordinates) and ADM methods (finding stimulation locations that maximize electric field strength within a single spherical ROI), the TANS method not only increased stimulation to target regions but also reduced stimulation to non-target regions, proving that this method improves stimulation specificity during TMS, making it more targeted. Additionally, some researchers have used pfMRI methods to investigate functional network characteristics in patients with specific symptoms. For example, Gordon, Scheibel et al. (2018) explored the relationship between traumatic brain injury (TBI) and white matter integrity, RSFC, and posttraumatic stress disorder (PTSD), finding that reduced individual functional connectivity strength was associated with PTSD symptom severity, and that RSFC and white matter integrity could jointly explain 41% of the total variance in PCL-5 scores. Laumann et al. (2021) investigated functional network organization characteristics in patients with perinatal stroke, finding damage to the primary motor cortex in stroke patients and obvious posterior shifts in brain region activation during motor tasks. Meanwhile, patients' functional networks were reorganized, mainly occurring in frontal and parietal association regions. In summary, pfMRI methods have

shown good application prospects and therapeutic effects in clinical fields and should be given attention in future patient diagnosis and treatment.

4 Summary and Outlook

In summary, pfMRI methods have achieved certain research findings in investigating individual differences in functional network organization, individual identification, functional localization of local regions, identification of individual network hubs, development and plasticity of individual functional networks, and clinical applications, demonstrating unique advantages over group-average fMRI research and being important for revealing basic principles of brain cognition and diagnosing and treating major brain diseases. However, research in this field still has certain limitations in terms of research questions and methods that need to be addressed in future studies, such as few studies exploring the relationship between individual functional network organization and behavior, the long scanning time required by pfMRI methods, and the limited application of pfMRI in task-state research and multimodal data fusion studies.

4.1 Relationship Between Individual Functional Network Organization Characteristics and Behavior Currently, numerous studies have used pfMRI methods to reveal the individual specificity of brain functional network organization from different levels and perspectives. These research findings remind researchers to pay attention to individual differences in brain function in scientific research and clinical applications, which has important theoretical and practical significance. However, based on current research findings, we still cannot determine the practical significance represented by these individual differences in brain function. One main reason is that many researchers have focused on whether brain functional networks have individual specificity but have not linked these features to actual behavioral performance. Even though a few researchers have noticed this issue, they have only conducted exploratory studies on the correlation between individual brain network features and behavior without making it a key focus for in-depth investigation (Bergmann et al., 2020; Dworetsky, Seitzman, Adeyemo, Smith, et al., 2021; Kong et al., 2019; Seitzman et al., 2019; Yang et al., 2022). Moreover, these studies were mostly conducted with small samples, which may have stability issues in their results. Therefore, using pfMRI methods to explore the relationship between individual functional network characteristics and behavioral performance will be an important direction for future research.

4.2 Reducing Scanning Time Required for pfMRI For pfMRI methods, a widely recognized limitation is the need for long scanning times. As mentioned earlier, at least 40 minutes of low-motion data are needed to achieve reliable estimation of cortical functional connectivity, while subcortical structures and temporal lag analysis require even larger data quantities. This leads to at least two problems: First, fMRI is overly sensitive to head motion, requiring participants to keep their heads still during scanning. Long periods of head

immobility are difficult for individuals, especially special populations (such as patients, children, and elderly who often show increased head motion), which increases the difficulty of data collection (Gratton, Kraus, et al., 2020). Second, fMRI scanning is expensive, and long-duration data collection is not economical. In summary, this issue is a serious obstacle to the popularization and application of pfMRI methods.

Currently, for the head motion control problem in fMRI, some researchers have proposed strategies to minimize subject head motion and improve data quality, such as dividing data collection into several shorter sessions (Bergmann et al., 2020; Noble et al., 2017) or using online head motion estimation during data collection (Dosenbach et al., 2017). Additionally, there are two approaches to solving the problem of excessively long scanning times required by pfMRI. One approach is to reduce the data quantity demand of pfMRI, i.e., exploring methods to obtain relatively stable individualized results with small amounts of data. In this regard, some important progress has been made in recent studies. For example, Kong et al. (2019) proposed using a multi-session hierarchical Bayesian model (MS-HBM) to estimate individualized cortical networks, finding that when only 10 minutes of data were used, the homogeneity of cortical parcellation obtained was consistent with that in studies by Wang et al. (2015) and Gordon et al. (2017) using 50 minutes, and network parcellation based on this method showed better alignment with task activation. Additionally, some studies have found that multi-echo sequence fMRI can improve the sensitivity of BOLD signals (Bhavsar et al., 2014) and can be used to identify and discard non-neuronal fMRI signals (Power et al., 2018). Therefore, Lynch et al. (2020) speculated that it could improve the reliability of individual functional connectivity and verified this, finding that 10 minutes of multi-echo sequence fMRI data combined with principal component analysis denoising methods (Kundu et al., 2012) could obtain relatively stable estimates of individual functional connectivity.

The other approach is to increase the amount of data obtained per unit time of fMRI scanning, i.e., obtaining more data in the same scanning time. Multi-band fMRI technology, which has been widely used in some recent short-duration fMRI studies, can achieve this goal (Glasser et al., 2013; Miller et al., 2016). This technology can improve fMRI temporal resolution and the amount of fMRI data collected within a fixed time period by simultaneously scanning different brain locations. For example, when the multi-band acceleration factor is set to 4, the traditional 2-second repetition time (TR) can be shortened to one quarter, thereby tripling the amount of data collected in the same time. For example, the study by Wang et al. (2021) introduced earlier used multi-band fMRI scanning to reduce TR to 392 ms, enabling collection of sufficient data in about 15 minutes. Overall, researchers have attempted to overcome the problem of long scanning times in pfMRI research through improvements in head motion control, data analysis methods, and fMRI imaging methods, and have achieved preliminary progress. However, future research in this direction still needs further exploration. For example, in explorations to reduce pfMRI data

quantity requirements, whether the methods of Kong et al. (2019) and Lynch et al. (2020) are also applicable to estimation of other metrics such as eFC and network variants has not yet been verified. On the other hand, multi-band technology that can increase the amount of data obtained per unit time may also have the problem of reducing data signal-to-noise ratio, and this situation becomes more serious with increasing multi-band acceleration factors (Risk et al., 2021; Srirangarajan et al., 2021). However, pfMRI data quantity requirements may increase with decreasing signal-to-noise ratio. Therefore, future research should explore the relationship between pfMRI data quantity requirements and multi-band acceleration factors to find a balance between them, thereby achieving the goal of shortening pfMRI scanning times. In summary, solving these problems is undoubtedly important for the widespread application of pfMRI methods.

4.3 Attempting to Apply pfMRI to Task-State fMRI Research To date, most studies using pfMRI methods have targeted resting-state fMRI data, with main focus limited to brain functional networks. The main reason for this phenomenon is still the high data quantity requirement of this method. Among the studies reviewed in this article, most used publicly available pfMRI datasets. This data sharing greatly reduces researchers' costs in scientific research, but creating similar task-state fMRI datasets is more difficult (because different scientific questions involve differences in task types or task details). Additionally, conducting long-duration fMRI scanning on subjects in task states is not easy, as task requirements, noise, and other factors often make it difficult for participants to tolerate long fMRI scanning. Therefore, only a few task-state studies have used pfMRI methods, such as Salehi et al. (2020) revealing differences in functional network organization between different task states, and Porter et al. (2023) further identifying task states through functional network organization. However, the themes of these two studies were still limited to brain functional network organization. Recently, Mei et al. (2022) collected pfMRI data from 6 subjects during a perceptual sensitivity task (approximately 6 hours per subject), revealing the neural basis of unconscious information processing and proving that brain regions involved in conscious and unconscious processing overlap to some extent (such as frontoparietal cortex, which was previously considered to correspond to conscious processing in group-average research). This study represents an important breakthrough in applying pfMRI methods to task-state fMRI research, demonstrating the unique advantages of this method. Therefore, future research should target appropriate scientific questions, combine the data acquisition (multi-session scanning), data analysis, and imaging techniques mentioned in Section 4.2 to reduce pfMRI data requirements, and attempt to apply pfMRI methods to task-state fMRI research to promote the popularization and application of this method in brain science research.

4.4 pfMRI and Multimodal Data Fusion Research As mentioned in Section 2 of this article, some classic pfMRI datasets typically include multi-

modal data (such as structural images, behavioral assessments, gene expression, and metabolic indicators). However, most current studies have only focused on resting-state data, with only a few studies conducting exploratory integrated analysis of multimodal data. For example, Poldrack et al. (2015) found that functional connectivity in the resting state was highly correlated with some gene expression modules and amino acid concentrations in the human body. The research results of Gordon et al. (2017) also suggest that individual differences in functional network organization may originate from changes in brain structure. Although researchers in these studies did not conduct in-depth discussion and analysis of their multimodal integration results, their significance lies in inspiring us about the potential relationships between different modal data, prompting researchers to generate new meaningful hypotheses based on different scientific questions and promoting new pfMRI and multimodal data fusion research. Future research in this direction can not only further improve the reliability and accuracy of pfMRI through mutual verification of multimodal data but also deepen our understanding and knowledge of basic brain functions and their principles through complementary information from multiple modalities.

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