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Individualized brain mapping for navigated neuromodulation

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Abstract

The brain is a complex organ that requires precise mapping to understand its structure and function. Brain atlases provide a powerful tool for studying brain circuits, discovering biological markers for early diagnosis, and developing personalized treatments for neuropsychiatric disorders. Neuromodulation techniques, such as transcranial magnetic stimulation and deep brain stimulation, have revolutionized clinical therapies for neuropsychiatric disorders. However, the lack of fine-scale brain atlases limits the precision and effectiveness of these techniques. Advances in neuroimaging and machine learning techniques have led to the emergence of stereotactic-assisted neurosurgery and navigation systems. Still, the individual variability among patients and the diversity of brain diseases make it necessary to develop personalized solutions. The article provides an overview of recent advances in individualized brain mapping and navigated neuromodulation and discusses the methodological profiles, advantages, disadvantages, and future trends of these techniques. The article concludes by posing open questions about the future development of individualized brain mapping and navigated neuromodulation.

Keywords: Brain atlas; Individualization; Navigated neuromodulation; Multimodal magnetic resonance imaging; Transcranial magnetic stimulation; Deep brain stimulation

Introduction

The human brain is the most complex organ in terms of structure and function, making brain atlases essential tools for studying its intricacies.[1–6] Brain atlases not only enable researchers to understand complex functional circuits and the neural basis of cognitive behaviors but also provide insights into development mechanisms, identification of early diagnostic biomarkers, and the establishment of personalized and precise treatments for brain diseases.[7,8] In the past decade, neuromodulation techniques[9,10] such as transcranial magnetic stimulation (TMS)[11] and deep brain stimulation (DBS)[12] have rapidly advanced, enabling personalized treatments for various neuropsychiatric disorders. These techniques can improve patient outcomes by precisely targeting specific brain regions or circuits, altering neuroelectrical activity and transmitter release.[13,14]

Recent advancements in neuroimaging and computer-assisted intervention have led to new concepts like stereotactic neurosurgery and neurosurgical navigation systems. While these technologies have made substantial advancements in the treatment of brain diseases, they are confronted with a formidable challenge—the pronounced variability in pathological mechanisms and individual patient differences shaped by a complex interplay of genetic and environmental factors.[15] This interplay results in structural disparities within the brain, encompassing differences in size, shape, cellular architecture, and brain connectivity. The uniqueness of each individual's brain structure extends its influence to brain function, leading to variability at behavioral levels, including functional signals,[16] cognition,[17] psychiatric symptom,[18] and clinical neurosurgery.[19,20] As a result, there is a need for personalized navigation solutions and targeted neuromodulation strategies for each disease and

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patient. Current commercial brain navigation systems often rely on traditional anatomical brain atlases, which have limitations due to their basis on postmortem specimens, insufficient information on individual variability, and lack of functional brain parcellation.[7,21] This hinders clinical effectiveness and the precision of neuromodulation therapies. A major bottleneck in navigation-based neuromodulation lies in the lack of fine-scale brain atlases and individualized approaches, limiting the development of personalized and precise treatments. Existing stereotactic navigation systems often require manual intervention, reducing efficiency and introducing potential subjective errors. Consequently, it is crucial to integrate and analyze individualized brain mapping methods for specific neuromodulation navigation, thus to better characterize pathological changes, understand neuromodulation mechanisms, and provide a basis for early diagnosis and prognostic evaluation.

In this review, we presented an overview of recent advances linking individualized brain mapping and navigated neuromodulation, focusing on establishing precise neuromodulation paradigms based on individualized brain mapping. We discussed the latest approaches to individualized brain mapping, their methodological profiles, advantages, disadvantages, and application trends. We also reviewed the progress in non-invasive neuromodulation technology, providing an overview of current TMS targeting methods and future directions. Furthermore, we illustrated how various DBS procedures localize stimulation targets and how the latest individualized brain mapping techniques promote DBS localization. Finally, we summarized our findings and posed open questions about the future directions of individualized brain mapping navigated neuromodulation.

Current Status of the Methodology for Individualized Human Brain Mapping

From initial attempts a hundred years ago[1] to recent advancements,[7,8] individualized brain mapping has experienced several stages as brain imaging techniques have evolved. The pioneering method[22] involved constructing a brain atlas using postmortem brain tissues from a single subject and manually labeling brain regions based on cytoarchitectural features. The most widely utilized atlas among these is the Brodmann atlas.[1,22] This first specimen atlas highlighted the potential of individualized brain mapping, but brain atlases based on an individual's anatomical characteristics lacked population commonality and provided only a coarse division of brain regions. More recent studies have employed staining techniques to map specimen brains at the group level, using cytoarchitectonic and myeloarchitectonic characteristics[4,5] extracted from multiple subjects. The increased number of subjects improved the population coverage of the brain atlas; however, anatomical annotation is labor-intensive, and the experience and annotation standards of annotators are not uniform, making it challenging to create a group-consistent brain atlas. Furthermore, since *ex vivo* manual annotation is invasive, histological brain atlases cannot be reproduced in living subjects. In this case, various individualization techniques [Figure 1, Table 1] have been employed in individualized brain mapping.

Registration-based individualized brain mapping

The most straightforward approach for individualized brain mapping is image registration. Regardless of the magnetic resonance imaging (MRI) data modality, the goal of single-modality registration is to align the reference atlas[21] to individual space and minimize reference-individual differences. The structure registration-based individualized brain mapping [Figure 1, Table 1] can depict local anatomical architecture like brain shape and volume size, but hardly assesses diffusion characteristics or functional activation patterns.[23] Diffusion registration-based individualized brain mapping [Figure 1, Table 1] can preserve diffusion characteristics, such as diffusion orientation and density, and is advantageous for tractography.[24] Function registration-based individualized brain mapping [Figure 1, Table 1] is to align functional MRI signals, ensuring a group-consistent functional activation pattern between subjects.[25]

The single-modality MRI registration-based individualized brain mapping depicts the parcellation pattern from a structural or functional perspective. To achieve a more comprehensive individualized brain mapping, multi-modality registration techniques were developed to integrate anatomical architecture, connectivity, and functional information of the cerebral cortex [Figure 1, Table 1] multi-modality registration).[26] In addition to the similarity constraint within the anatomical structure, multi-modality registration aims to minimize structural connectivity or functional connectivity differences between the reference and individualized atlases, allowing multi-modality features to be fused during the registration process. Compared to classical volume-based single-modality MRI registration techniques, surface-based multi-modality registration better preserves the biological features of the cortex.[26,27] However, surface-based multimodal registration is limited by substantial surface shape variability between individuals.[26] The structural connectivity and functional networks often differ even in the same cortical placement between subjects.

In addition to multi-modality registration techniques, multi-atlas registration [Figure 1, Table 1] offers another approach to individualized brain mapping.[28] While multi-modality registration combines parcellation characteristics from different MRI modalities, multi-atlas registration aims to integrate parcellation patterns from a group of reference brain atlases. Briefly, multi-atlas registration assigns reference atlas labels with the highest likelihood to a new subject, thereby constructing the individualized brain atlas. A typical multi-atlas registration framework includes reference atlas generation, atlas registration, label propagation, and label fusion.[28] Notably, the multi-atlas registration-based individualized brain mapping is sensitive to label fusion algorithms. Individualized brain mapping based on multi-atlas registration is also capable of integrating parcellation patterns from cross-modality reference atlases.[29]

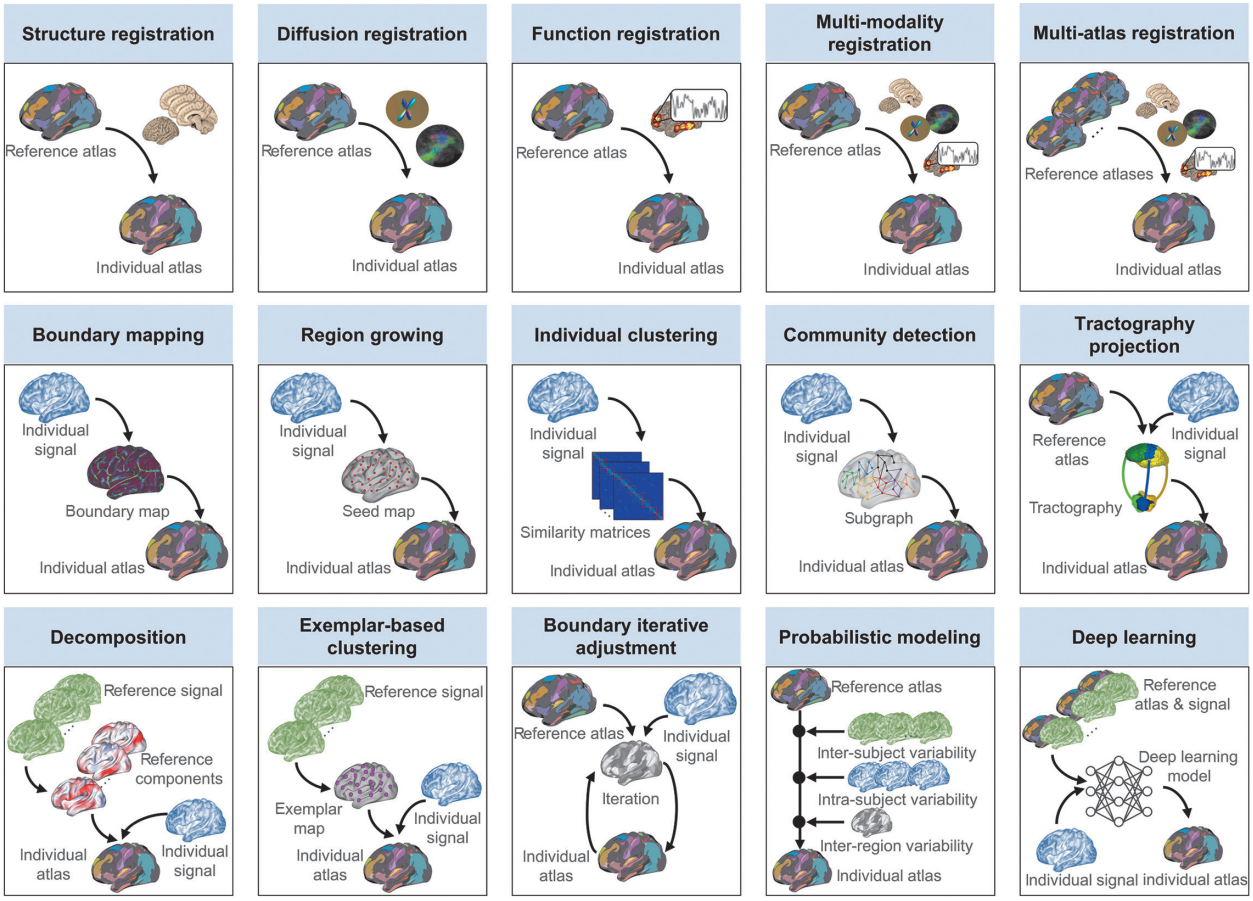

Figure 1: Schematic overview of individualized brain mapping techniques. A detailed description can be seen in Table 1.

In summary, while single-modality MRI registration methods could construct a non-invasive individualized brain atlas compared to histological labeling, they have insufficient parcellation perspective. Multi-modality MRI registration methods offer a comprehensive perspective by integrating cytoarchitecture, connectivity, and functional aspects into individualized brain mapping, but they encounter individual variability issues. Multi-atlas registration techniques provide a more flexible way to individualized brain mapping by fusing parcellation patterns from a group of reference atlases with single or multiple modalities. In the future, registration-based individualized brain mapping is likely to lean toward cross-modality multi-atlas registration, integrating with the burgeoning deep learning technology to develop a range of clinical applications.

Unsupervised learning-based individualized brain mapping

While image registration-based individualized brain mapping techniques have been widely used in clinical applications,[11,12] they have limited ability to accurately capture individual specificity. To better capture the individual specificity in brain mapping, unsupervised learning-based methods rely solely on the subject's own MRI data. The ultimate purpose of unsupervised learning-based individualized brain mapping is to segment structurally or functionally integrated brain tissues into segregated brain regions.[7] To achieve this goal, several unsupervised learning-based methods have been developed, which can be classified into four categories: boundary mapping,[6] region growing,[30] individual clustering,[31–33] and community detection.[34]

Inspired by edge detection algorithms in image segmentation studies, boundary mapping was initially used to identify locations where parcellation features change rapidly in the target ROI [Figure 1, Table 1].[6] These abrupt local changes in cytoarchitecture, connectivity, or function form the biological basis of boundary mapping.[6] Consequently, the boundary mapping method does not require setting the number of subregions, which is automatically determined by the distribution of the parcellation features. However, constructed brain atlases may be inconsistent when using different parcellation features due to variations in the distribution of boundary features. Notably, most unsupervised learning-based individualized brain mapping methods are not limited to parcellation features and MRI modalities.[7] Compared to seeking local boundaries where parcellation features change rapidly, the region growing method[30] [Figure 1, Table 1] starts from the central seed points in the target ROI and iterates outwards. The iteration is to find the voxels with the parcellation features most similar to the seed points or regions and merge them into the updated seed regions until the iteration traverses all voxels. These iterations are multi-channel, iterating from multiple seed

Table 1: Summary of individualized brain mapping techniques.

Categories	Items	Descriptions	Schemas
Registration-based individualized brain mapping	Structure registration[23]	Minimizing local structural differences between reference and individual atlases	Figure 1: structure registration
	Diffusion registration[24]	Minimizing differences in local diffusion characteristics or structural connectivity between reference and individual atlases	Figure 1: diffusion registration
	Function registration[25]	Minimizing differences in functional activation or functional connectivity patterns between reference and individual atlases	Figure 1: function registration
	Multi-modality registration[26]	Minimizing feature differences between reference and individual atlases across multi-modalities	Figure 1: multi-modality registration
	Multi-atlas registration[28]	Minimizing feature differences between multiple reference atlases and individual atlas	Figure 1: multi-atlas registration
Unsupervised learning-based individualized brain mapping	Boundary mapping[6]	Not limited to data modalities, but often used in fMRI to find where changes are sharpest as brain region boundaries	Figure 1: boundary mapping
	Region growing[30]	Not limited to data modalities, brain regions start at random centroids and expand outward until convergence to boundaries	Figure 1: region growing
	Individual clustering[31–33]	Not limited to data modalities, the mainstream unsupervised clustering methods are K-means, hierarchical clustering, and spectral clustering	Figure 1: individual clustering
	Community detection[34]	Not limited to data modalities, a graph theoretic approach is utilized to perform subgraph cuts to delineate brain regions	Figure 1: community detection
Group prior-guided individualized brain mapping	Tractography projection[35]	Only used for dMRI data, relying on reference atlas to offer seed brain regions for tractography between cortical and subcortical areas	Figure 1: tractography projection
	Decomposition[36,37]	Mostly used for fMRI data, utilizing a group of subjects to build the group-level reference components and then projecting it onto individual subjects	Figure 1: decomposition
	Exemplar-based clustering[38,39]	Mostly used for fMRI data, utilizing a group of subjects to build the group-level exemplar map and then performing affinity propagation clustering for individuals	Figure 1: exemplar-based clustering
	Boundary iterative adjustment[40,41]	Not limited to data modalities, utilizing a group of subjects to build a reference probability atlas and then iteratively adjusting the region boundary in individuals until convergence	Figure 1: boundary iterative adjustment
	Probabilistic modeling[42,43]	Mostly used for fMRI data, utilizing a group of subjects to optimize inter-subject, intra-subject, and inter-region variability and to build the individual atlas	Figure 1: probabilistic modeling
	Deep learning[44,45]	Not limited to data modalities, utilizing a group of subjects to train an individualized brain mapping model and then predicting the parcellation pattern for individuals	Figure 1: deep learning

dMRI: Diffusion MRI; fMRI: Functional magnetic resonance imaging.

points simultaneously. Thus, the parcellation granularity of the region growing method is determined by the number of seed points. Additionally, the final individualized brain atlas may be affected by the location of the initial seed points. Methodologically, boundary mapping and region growing are complementary, with the initialization of the former being the boundary and the latter being the central points.

Typical individual clustering algorithms applied in individualized brain mapping are K-means, hierarchical, and spectral clustering [Figure 1, Table 1]. K-means clustering assigns voxels to several centroids according to the principle of nearest distance, thereby assigning all voxels of the target ROI to a given number of clusters.[31] Hierarchical clustering aims to build a hierarchical relationship map according to the similarity between voxel or cluster pairs.[32] Spectral clustering first reduces the dimension of the parcellation features and then performs K-means clustering on the reduced-dimensionality feature matrix.[33] Community detection is a type of graph segmentation algorithm regarding the target ROI as an adjacency graph [Figure 1, Table 1].[34] The purpose of a community detection algorithm is to segment an adjacency graph into subgraphs by minimizing the distance within the subgraph and maximizing the distance between the subgraphs. Clustering pays more attention to the inherent attributes of nodes, whereas community detection focuses on the connections between nodes. Also, while clustering methods are sensitive to cluster numbers, community detection algorithms can estimate the optimal number of subgraphs.

Boundary mapping or region growing methods focus on local variability or continuity, while individual clustering and community detection methods pay more attention to the global relationship. Utilizing the subject's own MRI data rather than reference atlases, these unsupervised learning-based individualized brain mapping methods are advantageous in depicting individual specificity. In the future, there is an urgent need for unsupervised learning-based individualized mapping methods that can work with low-resolution diffusion MRI (dMRI) and short-scan functional magnetic resonance imaging (fMRI), which are commonly acquired in clinical settings. Additionally, as high-resolution dMRI and long-scan fMRI become more accessible, unsupervised learning-based individualized brain mapping will empower the neuroscience community to achieve substantial advancements beyond the current state.

Group prior-guided individualized brain mapping

Unsupervised learning-based individualized brain mapping methods effectively capture individual specificity in parcellation patterns, but their moderate population commonality, due to the lack of prior information from reference atlases, leads to challenges in depicting inter-subject consistency. Moreover, unsupervised learning-based methods,[7] with different settings, may produce highly variable parcellation results because of the absence of constraints from prior information. To address these issues, group prior-guided individualized brain mapping methods were proposed to integrate reference atlases with individual MRI data. Current group prior-guided individualized brain mapping methods include tractography projection,[20,35] decomposition,[36,37] exemplar-based clustering,[38,39] boundary iterative adjusting,[40,41] probabilistic modeling,[42,43] and deep learning.[44,45] These approaches employ prior information from group-level reference brain atlases to constrain or initialize the construction of individualized brain atlases. Consequently, group prior-guided individualized brain mapping can capture both high individual specificity and population commonality.

The tractography projection method depends on registering the reference cortical atlas to the individual brain and performing tractography between the subcortical seed ROI and cortical reference brain regions (Figure 1 & Table 1).[35] The ROI is then divided into reference-related functional zones based on the fiber connectivity profile. As fiber bundles connect functional circuits between cortical and subcortical regions, tractography projection-based individualized brain mapping aligns with neurological interpretation. This approach has been applied in localizing DBS targets.[20] However, the brain atlas constructed by tractography projection relies on an accurate reference cortical atlas and robust tractography algorithms. The reference cortical atlas is of great importance in giving credible interpretations of the delineation results. Since the reference cortical atlas is constructed by data from a group of subjects, it has strong population commonality but weak individual specificity. Whereas subjects differ because of their pathological states and brain anatomy, using the reference atlas to substitute for the individual's brain parcellation pattern may lead to inaccurate brain mapping results. Hence, developing an accurate cortical brain atlas of an individual subject is a necessary step before building an individualized subcortical atlas by tractography projection. In terms of tractography algorithms, false positive fiber bundles and fiber crossing issues may also compromise the tractography-based projection's performance. To enhance the tractography algorithms, high spatial resolution dMRI data has been utilized to create tractography projection-based individualized brain mapping.[20] In the future, the availability of clinically oriented high-field MRI technology may further advance this individualization method.

The decomposition methods first generate group-level components [Figure 1, Table 1],[36,37] then calculate each subject's loading matrix on the group-level components, and finally map the loading matrix to the corresponding brain spatial location to create an individualized brain atlas. But there are negative loadings that may not be biologically meaningful. To prevent negative loadings, a group-guided non-negative matrix factorization (NMF) method was proposed.[37] However, the individual loading matrix's sensitivity to group-level component generation makes group prior-guided decomposition methods vulnerable to the number of subjects and the dimension of parcellation features.[37] More recently, an autoencoder model has been employed to extract group-level components in a non-linear manner, providing an individualized brain atlas with flexible parcellation granularities.[45]

Exemplar-based clustering builds upon traditional individual clustering while incorporating prior information from reference atlases [Figure 1, Table 1]. Researchers have used unsupervised learning-based individual clustering methods to construct an individualized brain atlas based on data from a specific subject; however, this approach may produce an individualized brain atlas that is sensitive to initial centroids and cluster numbers. To address this issue, exemplar-based clustering first identifies the most representative exemplars of a group of subjects using a greedy algorithm.[38] Then, it assigns a voxel to the exemplar-corresponding clusters by minimizing the distance to the determined exemplars. Similarly, group-guided affinity propagation clustering first finds the cluster centers and the optimal number of clusters in a group-level connectivity matrix.[39] Then, it uses the group-level results to initialize individual-level affinity propagation clustering. While exemplar-based clustering individualized brain mapping methods are robust in constructing highly individual-specific and inter-subject consistent brain parcellations, they are time-consuming and computationally complex.[38,39] Consequently, these methods may be more suitable for individualized brain mapping with low-dimensional parcellation features or small-volume ROIs. In the future, dimensionality reduction algorithms and parallel computing techniques may be employed to reduce computational burden and accelerate convergence.

Iterative boundary adjustment first creates a group-level reference atlas based on a large population dataset [Figure 1, Table 1].[40] The group-level reference atlas is then used as an initialization of individualized brain mapping. Each vertex or voxel is iteratively reassigned to the functional network with the most similar parcellation features until the iterative adjustment process converges according to a predefined criterion. This method is robust whether the parcellation features are functional connectivity[40] or structural connectivity.[41] Since the parcellation pattern of an iterative adjustment-based individualized brain mapping depends on a reference atlas, it is essential to construct canonical reference brain atlases.[21] Currently, the main technical challenge of iterative boundary adjustment methods is portability, as many empirical experiments are required to find the optimal termination criteria in different application scenarios. Furthermore, reference atlases constructed by normal subjects may not accurately reflect brain atrophy or dysconnectivity in patients. In the future, group-level age-specific and disease-specific brain atlases may enhance the clinical applicability of the boundary iterative adjusting method.

Probabilistic modeling methods use group-level parcellation features and labels as a prior probability distribution [Figure 1, Table 1].[42,43] To construct an individualized brain atlas for a new subject, the maximum posterior probability is calculated by maximizing the consistency within subregions and the difference between subregions. Earlier probabilistic modeling-based atlas focused on population-level parcellation patterns and inter-region variability. Later, inter-subject variability was introduced to the calculation of posterior probability.[42] Coupled with advancements in high-quality fMRI data, multi-session scanning has enabled researchers to consider intra-subject variability.[43] Probabilistic modeling methods are primarily used for fMRI data and allow the fusion of local and global parcellation features. Currently, the latest multi-session hierarchical Bayesian model (MS-HBM) has achieved impressive results for studying individual specificity at lab level.[43] However, applying the MS-HBM in clinical settings is challenging due to the requirement for high-quality MRI data, which necessitates long scanning times. In the future, data generation techniques may offer clinical feasibility for high-quality fMRI-based probabilistic modeling individualization methods.

Deep learning methods train classification or regression models using reference brain atlases and signals, and then test the trained models using a new individual's data to construct an individualized brain atlas (Figure 1 & Table 1).[44,45] These deep learning-based individualized brain mapping methods are not sensitive to parcellation features and data modality. In addition to benefiting from the powerful representation capacity of deep learning models, deep learning-based individualized brain mapping has been reported to be more capable of capturing individual variability than parameter-based group prior-guided methods.[44,45] However, as a "black box", the parcellation criteria of deep learning models are only weakly interpretable from a biological perspective. Moreover, the accuracy of deep learning models is data-hungry and relies heavily on the number of training samples and model complexity. Excessive attempts at adjusting hyper-parameters and overly complicated models may lead to overfitting. In the future, deep learning-driven individualization methods may be used in neuroscience research on large-scale datasets. Simultaneously, with the development of super-resolution technology, individual-level deep learning models, such as self-supervised learning, may become dominant in the field of individualized brain mapping.

By integrating individual parcellation features and reference atlases, group prior-guided individualized brain mapping methods can effectively capture both individual specificity and population commonality. These methods have not only made significant contributions to neuroscience research but have also demonstrated clinical feasibility in some cases. In the future, advancements in dimensionality reduction, parallel computing, population-specific brain atlases, data generation techniques, super-resolution MRI, and self-supervised learning will further accelerate the development of clinically useful group prior-guided individualized brain mapping.

Summary

In the present study, individualized brain mapping methods were divided into three categories. Registration-based individualization methods preserve population commonality to the greatest extent, while unsupervised learning-based individualization methods capture individual specificity to the greatest extent. By combining group priors with individual characteristics, group prior-guided individualized brain mapping methods retain not only high population commonality but also capture sufficient individual specificity. These three types of individualization

methods are well-developed and have been applied to various neuroscience research and clinical scenarios. In the future, several techniques may facilitate the development of individualized brain mapping. First, MRI data quality enhancement techniques will be crucial, as MRI data quality directly affects the performance of individualization methods and the accuracy of the constructed atlases. However, clinical MRI data often have poor spatial resolution and signal-to-noise ratios. Enhancing clinical data quality through algorithms can promote the efficiency of individual parcellation feature extraction. Second, the development of population-specific group atlases is essential. Most current reference atlases provide population-level features for healthy young individuals but largely ignore age variability and pathological differences in broader human brain populations. Establishing group-level brain parcellation patterns for different age groups and pathological states is vital, as aging and pathological conditions often result in nuclear atrophy and decreased fiber bundle connections, leading to unstable clinical localization data. Finally, individual-level individualization modeling will be a future direction for individualized brain mapping. Most current individualization models are at the group level, with all subjects sharing the same set of parameters in individualized brain mapping. This approach inevitably leads to spatial registration errors between the group prior and individual features, regardless of the registration method applied. Moreover, group optima in the pipeline parameters do not reflect individual-level optimal parameters for parcellation. A "one subject, one model" approach, providing subject-specific parcellation models as well as subject-specific parcellation pipeline parameters for each subject, will be the future direction of individualized brain mapping. In summary, individualized brain mapping is expanding and will continue to integrate into clinical practices, with even more exciting advancements expected in the near future.

Non-Invasive Neuromodulation Method: Electric Field Simulation Guided and Brain Circuits Targeted TMS

The previous section has focused on the state-of-art methodological review of individualized brain mapping [Figure 1, Table 1]. In the next section, we will discuss how individualized brain mapping approaches can be applied to the field of neuromodulation, specifically with regard to non-invasive neuromodulation using TMS. TMS is an established, safe, and effective non-invasive neuromodulation method that delivers focused magnetic pulses to the scalp, generating an electric field in the cortex and modulating neuroactivity in the targeted brain region.[46] TMS has been used to treat many neuropathic conditions, including depression,[47] migraine,[48] and obsessive-compulsive disorder[49] according to the US Food and Drug Administration (FDA). A specific TMS target that can significantly affect the brain circuits is required to achieve substantial therapeutic effects. This section focuses on individualized TMS targeting methods with depression being the primary focus because it is one of the most extensively studied diseases. Although the traditional therapeutic approaches, such as medication and psychotherapy, are effective in treating depression, they do not work for approximately 20%–30% of patients diagnosed with major depression disorder.[50] TMS was therefore proposed as an alternative therapeutic approach that directly affects neural activity and modulates neuroactivity in ways that differ from conventional approaches.[47] In TMS therapy, a precise individualized stimulation target is essential for effective treatment. In the following subsections, we will overview the typical methods for individualized TMS targeting and discuss the potential for future targeting techniques. These methods can be broadly categorized into four classes: the fixed distance method, which is simple and convenient but may not account for individual differences; the registration method, which accounts for individual differences in brain anatomy but not functional connectivity; the brain connectivity-based targeting method, which considers individual differences in functional connectivity; and the functional brain network-based targeting method, which considers the brain network affected by TMS. The first two methods are often utilized in clinical trials and are of an experimental nature, while the latter two leverage more advanced brain network analysis tools to understand the underlying mechanism of TMS therapy and thereby seek to obtain more precise individualized targets.

TMS targeting based on scalp landmarks

Lesion and imaging studies indicate that depression is pathophysiologically influenced by left prefrontal lobe dysfunction.[51] Accordingly, stimulation at 5 cm anterior to the motor cortical hand hotspot [Figure 2A] has been suggested as an effective target for the treatment of depression. This location, which is in the dorsolateral prefrontal cortex (DLPFC), has proved to be an effective therapeutic brain region for depression in subsequent research.[47] So, determining the position of the DLFPC has become an increasingly important step in navigated TMS therapy for depression. Due to its convenience and rapid effects, the 5 cm targeting method was subsequently employed in several large clinical trials. For instance, 301 medication-free patients underwent six weeks of stimulation[52] and 127 patients received three weeks of targeted stimulation.[53] However, some studies revealed that the 5 cm rule failed to locate the DLPFC in one out of three patients.[47,54] To improve targeting accuracy, a location more anterior to the hand hotspot, such as at 5.5 cm or 6.0 cm or even 7.0 cm [Figure 2A], was adopted to localize the DLPFC.[54,55] Although these methods are convenient, fast, and extensively used in clinical situations, researchers still found no standard distance that could accurately specify the location of the DLPFC since 5 cm, 6 cm, and even 7 cm distances all provide therapeutic effects on depression. Due to the variability in head size and shape, determining the distance in different subjects before stimulation remains challenging, which limits the application of the scalp landmarks method in TMS targeting and compromises their therapeutic efficacy.

TMS targeting based on individual anatomy

To alleviate the issue of scalp landmark variability across subjects, targeting methods based on individual

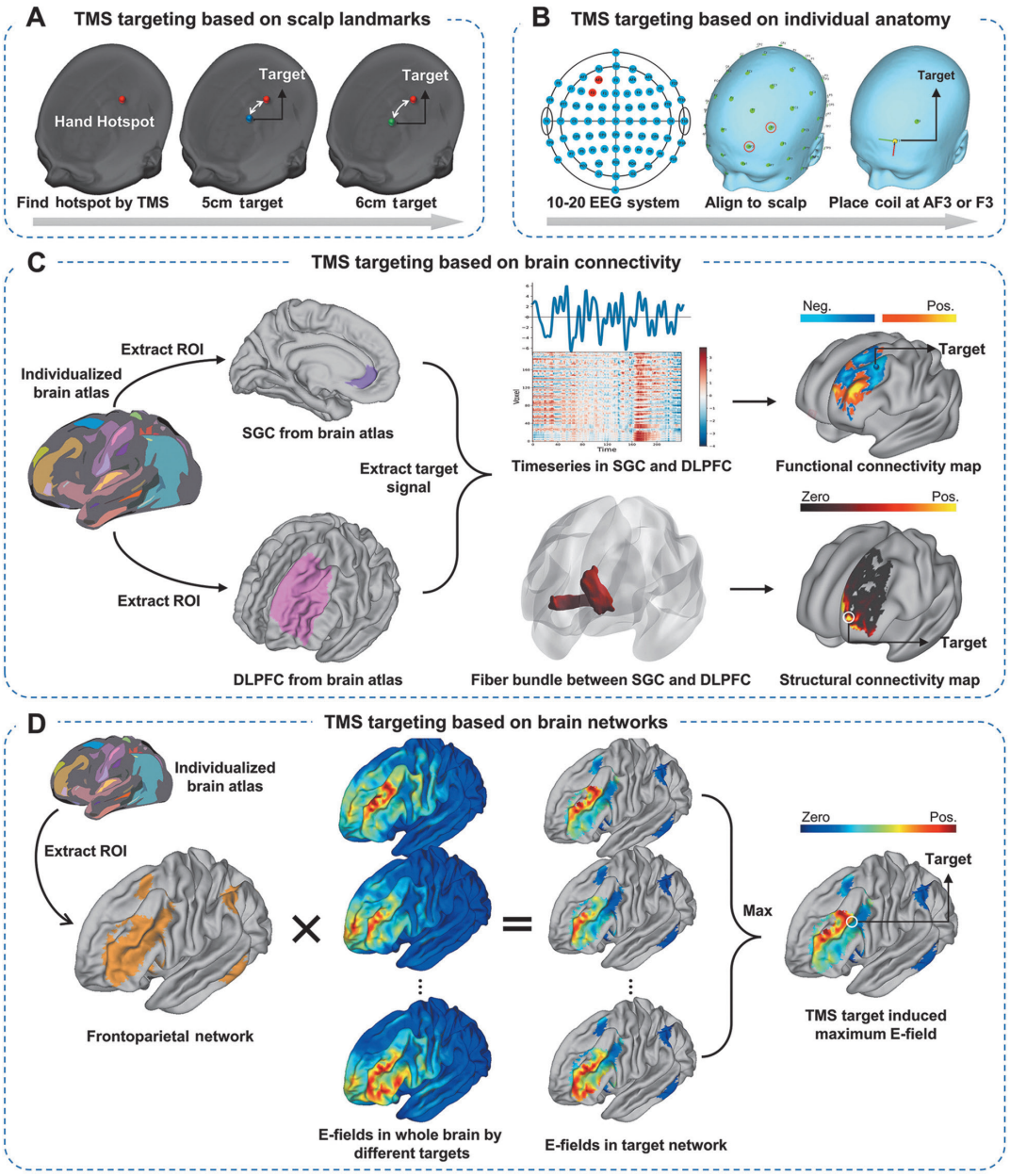

Figure 2: Overview of four different individualized TMS targeting methods. (A) TMS targeting based on scalp landmarks. Initially, the hand hotspot is identified by stimulating the motor region and assessing the resulting signal. In the illustration, the red point serves as a representative position for the hand hotspot. Additionally, the blue and green points represent the 5 cm and 6 cm targets, respectively. (B) TMS targeting based on individual anatomy. This figure depicts the 10–20 EEG system. These electrodes are firstly projected to the subject's scalp, and then the TMS coil is placed into the warrant position such as AF3 or F3 electrode that is commonly considered to be close to the DLPFC at the group level, and are marked by the red circles in the figure. (C) TMS targeting based on brain connectivity. The seed and target region are extracted from individualized brain atlas. The purple region represents the SGC, associated with depression, while the pink region represents the DLPFC, a potential target for stimulation. Functional timeseries are extracted from both of these regions, and functional connectivity is calculated using the extracted timeseries. This process yields the TMS target that exhibits the maximum anti-correlation with SGC within the DLPFC. Regarding structural connectivity, the fiber bundle passing through both of these regions is extracted and utilized to compute the structural connectivity. The subregion within the DLPFC with the greatest number of fibers is determined as the TMS target. (D) TMS targeting based on brain networks. The FPN is extracted from the individualized brain atlas. To attain the maximum E-field strength within the FPN, simulated TMS is repeatedly applied to FPN at various positions. The simulated E-field values are collected within the FPN, and the target that yields the highest cumulative E-field strength is identified as the TMS target. DLPFC: Dorsolateral prefrontal cortex; FPN: Frontoparietal network; SGC: Subgenual cingulate cortex; TMS: Transcranial magnetic stimulation.

anatomical images were proposed. These methods consist of two main steps: identifying the target on a reference atlas and projecting the group-wise target to the subject space using registration-based individualized brain mapping techniques mentioned in the above section. As image registration is quite well established and widely available in standard software packages, the majority of research in the field of TMS targeting methods has focused on determining the precise location of the DLPFC at the group level. Two types of representative studies are those that are based on electroencephalography electrode localizations and those that are based on brain atlases.

Early research verified that the electroencephalography (EEG)-F3 electrode in the 10–20 electroencephalography system [Figure 2B] coincides well with the DLPFC at the group level, and so the EEG-F3 is often chosen as the target (MNI coordinate: –51, 51, 44).[56] Subsequently, the group location of F3 can be projected to an individualized location and then used to determine the individualized TMS target through a registration of the anatomical volumes. A further study identified another target termed Fitzgerald (MNI: –45, 45, 35), which is located near the midpoint between the positions of the F3 and AF3 electrodes. This target was obtained by comparing the position of the EEG electrodes between the group DLPFC and the EEG electrodes across subjects and was verified to provide a better localization of the DLPFC.[55] Rusjan *et al*[57] also found evidence that a location between the F3 and F5 that was very close to the F5 overlapped with the DLPFC and verified that this target provided significantly less inter-subject variability than either the fixed distance method or the EEG-F3 method. However, all these targets require the availability of neuroimaging data and accurate registration of the subject anatomy. In this case, a method that can be used without the availability of neuroimaging data was proposed to determine the location of the F3 electrode by directly measuring a number of parameters related to the subject's head dimensions and calculating the location of F3 based on those parameters. This method, termed the Beam-F3 target,[58] has been extensively applied in clinical settings with greater reliability than the 5 cm target.[59] In addition, the brain atlas-based method can be also used to determine the location of the DLPFC, since almost all brain atlases include information about areas related to the DLPFC. For instance, the DLPFC overlaps with area 9 and 46 in the Brodmann atlas, and the center of the BA9 and BA46 border was identified as a potential TMS target.[60]

Compared with the fixed distance, targeting methods based on anatomical images show better consistency across subjects.[55] While many advances have been made in registration-based individualized brain mapping techniques, neither of them provides fully disease-specific targets for individual subjects as the DLPFC is documented to not only play a role in the development of depression but also other diseases, such as Parkinson's disease.[61] In addition, the DLPFC acts as a hub in a brain network with identified involvement in many activation studies and neuropathies.[62] Therefore, it will be useful to introduce network information about the DLPFC when attempting to identify the most appropriate individual TMS target.

TMS targeting based on brain connectivity

While stimulating the DLPFC via TMS is reported to be effective in the treatment of depression, Fox *et al*[63] found a significant negative correlation (anticorrelation) of functional connectivity between these DLPFC targets and the subgenual cingulate cortex (SGC). The SGC shown in Figure 2C was identified as an effective target for treating depression in DBS.[64] In this case, a potential therapeutic mechanism for the treatment of depression by stimulating the DLPFC by TMS was revealed. That is, the position with the most anticorrelation to the SGC may be regarded as an appropriate TMS target; this gave birth to the connectivity-based TMS targeting methods. Unfortunately, the SGC typically offers quite a low signal-to-noise ratio in fMRI studies. This causes the SGC to be an unstable target when relying on traditional seed-based methods. A seed map method was developed to improve the stability of the connectivity metric by replacing the average blood-oxygen-level-dependent (BOLD) signal of the SGC with the weighted average BOLD signal of the whole brain gray matter.[65] Furthermore, Cash *et al*[66] proposed a clustering method for determining the position of the voxels that are most anticorrelated with the signal in the SGC in cortical regions to improve the precision and reproducibility of the functional connectivity-based targeting. Using a combination of the seed map and the clustering method can reduce the targeting position difference between different days from 25 mm to approximately 2 mm across scans.[66]

Another type of method for computing the connectivity between brain regions involves dMRI. Here, tractography obtained from dMRI data was used to directly and structurally delineate the relationship between regions as described in the individualized brain mapping section [Figure 2]. Compared with BOLD Signal, tractography should be more consistent across scans because changes in structural connectivity are quite stable over short days. Hence, structural connectivity was utilized to determine an individualized TMS target that was located in almost the same position across scans.[67] In addition, the targets acquired by this method were near the group target and had no significant variance between subjects. Although localization based on structural connectivity has a preferable intra- and inter-subject consistency, it has a relatively weak functional interpretation of the therapeutic effect, while localization based on functional connectivity is more promising in this aspect.[67]

Most previous studies used fMRI to determine individualized TMS targets,[63,65,66] whereas fewer relied on dMRI.[67] The targeting position methods based on fMRI are reasonably validated as effective in clinical trials,[68] but they still lack reproducibility across scans.[69] In comparison, the targeting methods based on dMRI successfully solve the heterogeneity issues that are dominant in fMRI, but have thus far failed to achieve significant therapeutic effects.[67] Hence, future studies that integrate fMRI and dMRI data may enable a good interpretation of TMS effects as well as excellent consistency of TMS targeting. One potential way to integrate these is to use the structural connectivity obtained by dMRI to constrain functional connectivity such that noise can be suppressed while preserving the already identified therapeutic clinical effects. In addition, both functional and structural connectivity-based methods attempt to find the maximum connectivity between DLPFC and SGC in depression therapy, and so the choice of the SGC location also significantly affects connectivity-based methods. The SGC brain region identified by Fox *et al*[63] is a 5 mm radius sphere centered at the specified coordinate, while in the Brodmann map BN25 is the SGC brain region.[22] Furthermore, it is also important to determine the DLPFC brain

region, where the stimulation location is typically applied. Overall, the target SGC region and the directly stimulated cerebral cortex are determined based on the brain atlas. This underscores the vital role that individualized brain mapping, particularly the accurate delineation of the SGC brain region, plays in neuromodulation techniques like TMS.

TMS targeting based on brain networks

While localized regional dysfunction in the prefrontal cortex has been discovered before,[51] recent studies have shown that depression is also influenced by large-scale brain functional networks, especially the frontoparietal network (FPN).[70] Consequently, several targeting methods have emerged that aim to measure the engagement of the brain network affected by TMS. These approaches involved using individualized brain mapping techniques to construct functional brain networks related to depression, such as the functional registration or unsupervised learning-based method. As shown in Figure 2D, the region of interest (ROI) colored by orange is the FPN extracted from the individualized brain atlas.[70,71] Then, to achieve an optimal individualized TMS target to treat depression, it is worth studying to measure the influence of TMS on cortical tissues classified as belonging to the FPN and to identify the position with the maximum effect.

The most important metric related to the TMS effect is the electric field strength induced by TMS. Usually, many simulated stimulation targets are predefined in the target functional network, such as the FPN for depression, and then the electric field simulation is performed to obtain the simulated electric field corresponding to each stimulation target. Finally, the cumulative value of the electric field in the target network is calculated to generate the optimal stimulation target with the highest cumulative electric field value. The electric field simulation software uses SimNIBS (https://simnibs.drcmr.dk/),[72] which is an open-source software package that calculates the induced electric field induced by TMS based on the finite element method (FEM). Inspired by the method based on connectivity in the studies of Fox *et al*,[63,65] Opitz *et al*[73] adopted a creative method combining the simulated electric field with resting-state functional connectivity and quantifying impacts on directly and indirectly affected areas.[73] In the previous electric field simulation methods, this method can only register group-averaged functional networks to individuals due to the lack of individualized functional network maps, which results in the limitation of capturing individual specificity. It is worth noting that Lynch *et al*[19] acquired abundant personal functional MRI to construct precise individualized functional brain networks and demonstrate a better TMS influence *in silico* and *in vivo*.[19] In addition to the research described above, recent studies have used decomposition or deep learning methods [Figure 2] to obtain an individualized functional network—for instance, using non-negative matrix decomposition to divide the brain network into meaningful functional networks at the individual level[37] or computing the individualized functional networks utilizing a deep learning method.[45]

In addition to simulating electric fields, various methods employ the use of BOLD signal[74] and EEG signal[75] to gauge the effects of TMS on cortical tissue. These methods primarily consider that TMS stimulation not only directly affects the stimulated area but also ripples through the entire brain network. Consequently, these approaches define the brain's state changes and its input form to create a model of the brain, enabling the simulation of the propagation of TMS effects. Ultimately, after the propagation reaches a stable state, the alterations induced by stimulation at specific locations are quantified, and the stimulation site that promises the most significant expected changes is chosen as the target for TMS stimulation. These modeling methods necessitate dividing the brain into networks during the modeling process, with each network serving as a node of the model. While they are capable of identifying optimal TMS stimulation targets on a broader scale, developing personalized brain atlases is still necessary to provide an accurate pattern of an individual's brain network. Furthermore, all these simulations can be applied to all nodes within the brain network. Hence, they could be leveraged to explore additional disease-related targets beyond the DLPFC, such as the dorsomedial PFC (DMPFC) or the orbitofrontal cortex (OFC), as potential targets for the treatment of depression.[11]

Summary

In the preceding section, we have reviewed four primary approaches for pinpointing the target locations in TMS therapy, particularly in the context of treating depression. Although the fixed distance methods are fast, convenient, and have been adopted frequently in clinical settings, they encountered issues related to inconsistency among individuals and a lack of individual specificity. TMS targeting strategies based on individual anatomical images could alleviate inter-subject variability issues but lacked disease-specific localization interpretation. To encompass the brain's activity information linked to specific brain disease, connectivity information was utilized to identify TMS targets. Although the connectivity-based targeting methods are of remarkable biological interpretation, they were limited by the identification accuracy of disease-specific deep brain nuclei. In this case, disease-specific functional cortical networks combined with electric field simulation techniques were adopted to identify optimal TMS targets. However, a major shortcoming of anatomy-based, connectivity-based, and network-based targeting is that they are sensitive to the accuracy of defined brain nuclei or networks. Therefore, a precise individualized brain atlas is of great importance to achieve reliable and personalized TMS targeting. In summary, each of these methodologies possesses its own set of advantages and limitations. The ultimate objective remains the identification of fine-grained and disease-specific individualized TMS targets, fostering a more profound understanding of and improved treatment for various neuropsychiatric conditions. To achieve this goal, integration between multimodal neuroimaging and individualized brain mapping will consequently improve the accuracy as well as reproducibility of TMS targeting.[11,19] In addition, the

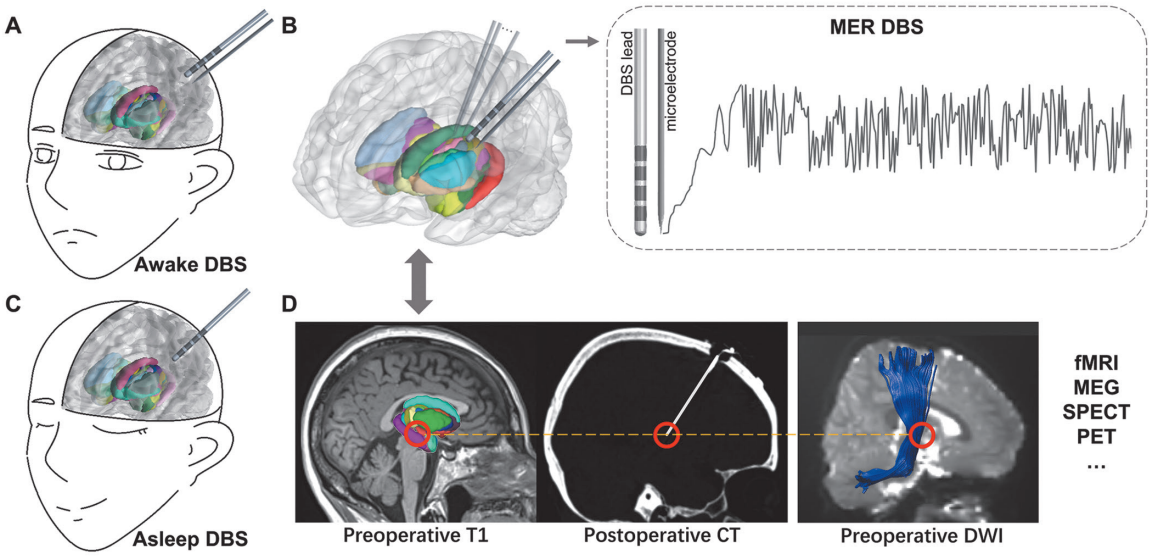

Figure 3: Awake DBS surgery *vs.* asleep DBS surgery. (A) Awake DBS surgery is usually performed with patients under local anesthesia and in a conscious state. Patients must remain awake during lengthy surgeries to provide intraoperative feedback to guide the surgeon in adjusting the DBS target. (B) The microelectrodes are implanted in the brain prior to or in parallel with the DBS leads using the planned trajectories. The MER DBS surgery continuously adjusts the microelectrodes intraoperatively according to the recorded electrode signals to determine the final DBS target locations. (C) Asleep DBS surgery is performed with patients under general anesthesia, usually without MER. Patients have a more comfortable surgical experience with a much shorter (compared to awake DBS surgery) surgical duration. (D) Asleep DBS surgery usually relies on neuroimaging for the preoperative target selection and postoperative target localization. High anatomical resolution T1 and geometric resolution CT images are often fused to perform MRI/CT DBS surgeries. dMRI enables direct targeting of WM fibers by tractography algorithms. Other neuroimaging categories (fMRI, MEG, etc.) can also play a role in DBS surgery. CT: Computed tomography; DBS: Deep brain stimulation; dMRI: Diffusion MRI; DWI: Diffusion-weighted imaging; fMRI: Functional magnetic resonance imaging; MEG: Magnetoencephalography; MER: Microelectrode recording; MRI: Magnetic resonance imaging; PET: Positron emission tomography; SPECT: Single photon emission computed tomography; WM: White matter.

development of deep brain TMS coils may provide more diverse stimulation methods, thus facilitating targeting accuracy and clinical outcomes.[76] These software and hardware efforts will continue to advance TMS targeting and facilitate the development of more personalized treatments.

Invasive Neuromodulation Methods: Localization Errors and Brain Atlas Solutions in Navigated DBS

DBS is a practical, interdisciplinary neurosurgical treatment that differs from cortical-oriented TMS as it directly stimulates subcortical nuclei using implanted electrodes. DBS has been employed to address a range of neurological and psychiatric disorders.[77] Common stimulation targets for DBS include subcortical nuclei associated with the basal ganglia-thalamo-cortical circuit, specifically the sensorimotor region of the subthalamic nucleus (STN), the internal part of the globus pallidus (GPi), and the ventral intermediate nucleus (VIM) of the thalamus.[78] Although these targets are typically millimeter-scale, precise stimulation can lead to significant improvements in related brain networks. Awake DBS surgery involves electrode implantation using microelectrode recording (MER) and intraoperative test stimulation with patients in an awake state.[79] In contrast, asleep DBS surgery is performed under general anesthesia without neurophysiological recording or stimulation, relying instead on intraoperative imaging techniques like computed tomography (CT) or MRIto guide electrode implantation.[79] The following subsections will delve into these two types of DBS surgery and their respective electrode implantation methods.

Awake DBS

Awake DBS surgery [Figure 3A,B] is performed under local anesthesia. Before electrode implantation, the stimulation target is roughly determined using histological human brain atlases. During surgery, the precise location of the stimulation target is further refined based on electrophysiological patterns of the neuroanatomical structures encountered along the surgical trajectory toward the DBS target. These patterns are produced by neuronal cell firing and can be estimated by recording extracellular and local neuronal activity using MER.[80] Based on the observed electrophysiological patterns, the stimulation target and electrode implantation trajectories can be well defined. Intraoperative awake patient responses can also contribute to adjustments during electrode implantation. Furthermore, intraoperative stimulation offers valuable physiological information to avoid acute clinical responses and side effects.

Electrode localization accuracy is a critical factor for DBS treatment efficacy.[81] A direct measurement of this accuracy is the radial error between the position of the implanted electrode and the expected target, serving as an objective numerical indicator of whether the DBS electrode is within-target or off-target. The histological human brain atlases attempt to standardize deep brain nuclei that are not well-visualized on conventional imaging sequences by using x, y, and z coordinates relative to the anterior conjoined-posterior conjoined (AC-PC) plane.[79,82] These atlases are constructed from a limited population of specimens and may not generalize well to the broader population. They are also susceptible to

spatial distortion due to unavoidable standardization and alignment errors in fixation, sectioning, and staining. Additionally, the location, shape, and extent of deep brain nuclei vary significantly across individuals.[82,83] Consequently, histological atlas-guided DBS localization cannot always provide precise stimulation targets for patients. It has been reported that the estimated radial error between the implanted electrode position of MER-guided awake DBS surgery and the expected target typically ranges from 1.0 mm to 1.4 mm,[84] while the mean overall radial error of neuroimaging-guided asleep DBS surgery ranges from 0.6 mm to 1.3 mm.[79] Besides localization error, the lengthy surgical time of awake DBS surgery is a significant burden on both patients and doctors, increasing the probability of infection during and after surgery. Increased risks of intracranial hemorrhage and reduced cognitive performance have also been associated with intraoperative MER. As a result, preoperative neuroimaging is now commonly used as an adjunct to enhance DBS localization by optimizing stimulation targets and electrode implantation trajectories. With the advancement of neuroimaging techniques, an increasing number of neuroscientists and neurosurgeons are shifting their focus toward asleep DBS surgery.

Asleep DBS

In contrast to awake DBS surgery, asleep DBS surgery is performed under general anesthesia without neurophysiological recording or stimulation, as depicted in Figure 3C,D. Although MER can also provide electrical signal feedback during asleep DBS surgery, it is currently avoided due to additional risks and debates surrounding its efficacy.[85] Instead, asleep DBS surgery relies on preoperative neuroimaging to determine the target location and verify the accuracy of electrode implantation. The high spatial resolution and individual specificity of preoperative neuroimaging serve to increase electrode implantation accuracy, eliminating the need for physiological feedback during awake DBS surgery. Moreover, asleep DBS allows for shorter surgery duration, reducing the infection risk for patients and alleviating the burden on surgeons compared to awake DBS surgery. Asleep DBS can be categorized into three main classes based on the modality of neuroimaging used: structural MRI/CT-guided, structural MRI/dMRI-guided, and other neuroimaging-guided.

In structural MRI/CT-guided asleep DBS, the stimulation target is identified using structural MRI and CT.[86,87] Due to significant heterogeneity across subcortical nuclei,[82,83] high-resolution structural MRI allows for direct identification of many subcortical nuclei with high tissue contrast. As a result, sMRI is the primary technique for preoperative target localization and trajectory planning.[86] Before the electrode implantation, the target nuclei could be localized by structure registration from a template atlas [Figure 1, Table 1] or manual outlining. Since structure registration is not a complete substitute for individual characteristics and manual outlining is time-consuming and laborious, robust individualized brain mapping is urgently needed to provide reliable targeting of nuclei. During DBS surgery, it is crucial to check whether the implantation location is within-target or off-target to adjust the electrode and verify accuracy. Since radio frequency pulses heat the DBS electrodes and pose safety issues, MRI scanning is not applicable after electrode implantation. Although the electrode-heating effect can be limited under certain scanning conditions,[88] signal gaps and artifacts remain major unresolved issues.[87] In this case, highly geometrically accurate CT images are beneficial for detecting the electrode location in the brain after implantation. Another advantage of using CT for intraoperative or postoperative imaging is its reduced scanning time and higher safety compared to sMRI (CT: 1 min; sMRI: 10 min[87]), which is advantageous for subsequent patient recovery. Consequently, the fusion of preoperative sMRI images with intraoperative or postoperative CT images has become one of the most popular techniques for guiding DBS electrode implantation with high accuracy. Although the fusion process increases technical and procedural complexity and may introduce fusion errors, many advanced image fusion algorithms have been developed to address this issue robustly.[86,87] In clinical settings, several stable software options for sMRI/CT fusion have been developed, such as Neuroinspire (Renishaw, Chassieu, France) and Framelink (Impex Inc, FL, USA). Lead-DBS is also an excellent tool for sMRI/CT fusion and further neuroscientific research.[89]

In the structural MRI/dMRI-guided asleep DBS, the stimulation target is identified using tractography. Tractography can be used to estimate the connectivity between nuclei and cortical functional zones.[20,90] For example, the stimulation target clinically considered most effective for dystonia, the ventral GPi, is motivated by its robust connectivity with the primary sensory cortex and posterior motor cortex.[91] To determine a subject-specific stimulation target, the most common individualized brain mapping method currently used in clinical practice is to register reference functional cortical atlas and subcortical ROI to the dMRI space and perform tractography [Figure 1, Table 1]. As mentioned in the tractography projection subsection, this method results in stimulation targets that are consistent across subjects, but may ignore individual differences in target localization caused by personalized disease states and diversity of brain anatomy. Since the stimulation targets are determined according to the cortical functional zones that the fiber bundles are connected to, an accurate individualized cortical brain atlas is of great importance in improving localization accuracy. Based on the individualized brain atlas, the location of the volume of tissue activated (VTA) could be determined with reasonable connectivity interpretation. The VTA can also be estimated by activating expected target locations with standard DBS parameters. Notably, patient-specific simulation of VTA should make more sense since a unique subject has a specific anatomical structure and brain morphology.[92] While tractography projection offers neuroanatomical connection guidance for DBS electrode localization, it is limited by technical issues, including poor spatial resolution, fiber crossing, and the presence of false positives during fiber tracking.[93] Furthermore, the group-level reference functional cortical atlas and subcortical ROI may not be suitable for all subjects due to individual variability among different people with

different pathological states and ages.[18] This individual variability may reduce localization accuracy. In addition, it is not clear whether the effective area of stimulation for DBS is the subcortical nuclei, or the cortical networks, or the fiber tracts.[94] In the future, more capable individualized brain mapping techniques are toward addressing this shortcoming of tractography-based DBS targeting and providing more robust and precise localization of targets. These advances would help to further optimize and personalize DBS treatment for patients, potentially leading to even better clinical outcomes.

fMRI guided DBS localization focuses on detecting and estimating the neurophysiological effects of DBS stimulation during or after electrode implantation, which serves to adjust the electrode location. These neurophysiological effects are often measured by the changes in the functional activation network within the basal ganglia or functional connectivity between the basal ganglia and the cortex. In particular, evidence from pig studies indicates that effective DBS treatment can target motor-related circuits and facilitate better cognitive and emotional circuit function.[95] The authenticity of the postoperative fMRI signal may be an issue because the implanted electrodes can cause susceptibility artifacts, which are highly problematic for robust and distortion-free fMRI recordings. Notably, low-conducting graphene electrodes have recently been adopted for use in STN-DBS, bringing few-to-no MRI artifacts and better control of heating due to distributed impedance while maintaining a high charge injection capacity.[96] Another work regarding graphene electrodes from the group of INBRAIN Neuroelectronics (Barcelona, Spain) is that they used graphene electrodes to record neurophysiological signals and pinpoint epileptic foci by recognizing abnormal discharge patterns.[97] While intraoperative or postoperative fMRI is used to evaluate the effect of stimulation, preoperative fMRI is also used to predict the optimal settings of the stimulation parameters for surgical planning.[98] In addition to the above three types of MRI-guided DBS electrode localization, positron emission tomography (PET),[99] single photon emission computed tomography (SPECT),[100] and magnetoencephalography (MEG)[101] are also adopted for searching the optimal stimulation target. Yalaz *et al*[102] used MEG to non-invasively detect the position and orientation of DBS electrodes. Although the average detection accuracy of the electrode location was 2.2 mm due to the insufficient measurement accuracy of the MEG system, future magnetometry systems with higher measurement accuracy may serve to more precisely detect the position and orientation of DBS electrodes.[99]

Summary

The transformation from MER-guided awake DBS surgery to neuroimaging-guided asleep DBS surgery has indeed led to reduced surgical duration and improved surgical efficacy. Preoperative neuroimaging techniques provide more precise stimulation target localization for DBS surgery compared to MER, and this accuracy is crucial for successful treatment outcomes. Various neuroimaging techniques are now applied in preoperative electrode localization, and advancements in stereotactic frameworks, including robot-assisted neurosurgery systems, have further enhanced the accuracy of electrode implantation.[80] In terms of DBS electrodes, there is a shift from traditional toroidal DBS electrodes, which produce a spherical electric field, to more advanced directional DBS electrodes.[104] These directional electrodes allow for more spatially flexible stimulation of the target. Graphene electrodes have improved the safety and signal-to-noise ratio of DBS electrodes. Rechargeable DBS systems have also been developed and utilized in the latest years, such as the G102RZ DBS system developed by PINS (Beijing PINS Medical Co. Ltd, Beijing, China). Currently, group reference brain atlases are still used to initialize the stimulation target and check whether the VTA exceeds the defined stimulation area. Although these group atlases have stable and consistent parcellation patterns within the same group of subjects, they may not provide sufficient identification of individual stimulation targets due to inter-individual variability caused by factors such as pathological states and ages. To address this limitation and enable the full utilization of advancements in surgical and electrode systems, a fine-grained individualized brain atlas is needed to provide precise stimulation targets with high individual specificity. In the future, combining individualized brain mapping techniques with DBS target localization will not only improve the accuracy and success rate of surgery but also contribute to a more personalized and effective treatment approach for patients.

Conclusions

Above, we have overviewed the methodology of current individualized brain mapping techniques and the target localization methods for two mainstream neuromodulation techniques. Here, we predict future directions by quickly discussing some open questions for individualized brain mapping navigated neuromodulation. (1) What is the required accuracy of individualized brain mapping for targeting neuromodulation? (2) Is volume-based, network-based, or connectivity-based individualized brain mapping most appropriate for navigation during neuromodulation? (3) How can individualized brain mapping be used for navigation neuromodulation in patients with different brain disorders and within different age groups? (4) How can individualized brain mapping be used for optimizing stimulation parameters for neuromodulation? (5) How can individualized brain mapping be used to estimate neuromodulation effects? (6) How can individualized brain mapping be used to predict the prognosis after neuromodulation?

Computationally, advancements in high-resolution imaging, machine learning algorithms, and real-time data processing are fundamental in this endeavor. The creation of brain atlases that seamlessly integrate multiple modalities as well as the development of adaptable simulation algorithms capable of accommodating diverse brain disorders and age groups is paramount. Furthermore, computational modeling should embrace individualized brain mapping and simulation to predict the potential effects of neuromodulation and post-neuromodulation prognosis effectively.

Neurosurgically, patient-specific brain characteristics and pathologic data need to be accurately collected preoperatively. Intraoperative surgical navigation could rely on individualized brain mapping and simulation, which could improve treatment outcome and reduces surgical risk. Postoperatively, the prognostic data of each patient should be carefully investigated and organized. All these patient-specific data from different centers should be legally collected and integrated for large-scale modeling and analysis to pursue the nature of optimal individualized treatment.

Regarding the animal models, they could serve as valuable tools for validating accuracy and assessing the safety of different individualized brain mapping techniques for specific neuromodulation. These animal models could also aid in comprehending how age-related and disease-specific changes in the brain influence the effectiveness of neuromodulation techniques, offering essential insights for tailoring treatment strategies. Moreover, animal models would contribute to the identification of potential biomarkers indicative of treatment success or failure.

In summary, the successful application of individualized brain mapping in neuromodulation demands a multidisciplinary approach. Computational advancements, neurosurgical expertise, and validation through animal models collectively pave the way for more precise and effective neuromodulation strategies across a spectrum of brain disorders.

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