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Review Article

Emerging Techniques for the Personalization of Deep Brain Stimulation Programming

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ABSTRACT: The success of deep brain stimulation (DBS) relies on applying carefully titrated therapeutic stimulation at specific targets. Once implanted, the electrical stimulation parameters at each electrode contact can be modified. Iteratively adjusting the stimulation parameters enables testing for the optimal stimulation settings. Due to the large parameter space, the currently employed empirical testing of individual parameters based on acute clinical response is not sustainable. Within the constraints of short clinical visits, optimization is particularly challenging when clinical features lack immediate feedback, as seen in DBS for dystonia and depression and with the cognitive and axial side effects of DBS for Parkinson's disease. A personalized approach to stimulation parameter selection is desirable as the increasing complexity of modern DBS devices also expands the number of available parameters. This review describes three emerging imaging and electrophysiological methods of personalizing DBS programming. Normative connectome-base stimulation utilizes large datasets of normal or disease-matched connectivity imaging. The stimulation location for an individual patient can then be varied to engage regions associated with optimal connectivity. Electrophysiology-guided open- and closed-loop stimulation capitalizes on the electrophysiological recording capabilities of modern implanted devices to individualize stimulation parameters based on biomarkers of success or symptom onset. Finally, individual functional MRI (fMRI)-based approaches use fMRI during active stimulation to identify parameters resulting in characteristic patterns of functional engagement associated with long-term treatment response. Each method provides different but complementary information, and maximizing treatment efficacy likely requires a combined approach.

RÉSUMÉ: Techniques émergentes de personnalisation de la programmation de la stimulation cérébrale profonde. Le succès de la stimulation cérébrale profonde (SCP) repose sur l'application d'une stimulation thérapeutique soigneusement calibrée en fonction de cibles spécifiques. Une fois déterminés, les paramètres de stimulation électrique de chaque zone de contact des électrodes peuvent être modifiés. L'ajustement itératif des paramètres de stimulation permet de tester des réglages de stimulation optimaux. En raison de l'étendue de l'espace des paramètres, les tests empiriques actuellement utilisés portant sur des paramètres individuels basés sur une réponse clinique aiguë ne sont pas viables. Compte tenu des contraintes liées à la brièveté des visites cliniques, l'optimisation de la SCP est particulièrement difficile lorsque les caractéristiques cliniques des patients ne procurent pas, comme c'est le cas pour la SCP dans le traitement de la dystonie et de la dépression et pour les effets secondaires cognitifs et axiaux de la SCP dans le traitement de la maladie de Parkinson (MP), un retour d'information immédiat. Une approche personnalisée de la sélection des paramètres de stimulation est souhaitable, car la complexité croissante des appareils modernes de SCP a également augmenté le nombre de paramètres disponibles. Cet article entend décrire trois méthodes émergentes d'imagerie et d'électrophysiologie permettant de personnaliser la programmation de la SCP. La stimulation normative du connectome de base utilise de vastes ensembles de données d'imagerie de la connectivité normales ou adaptées à la maladie. L'emplacement de la stimulation pour un patient donné peut ensuite être modifié pour impliquer des régions associées à une connectivité optimale. La stimulation en boucle ouverte et fermée guidée par l'électrophysiologie exploite quant à elle les capacités d'enregistrement électrophysiologique des dispositifs modernes implantés pour individualiser les paramètres de stimulation, et ce, sur la base de biomarqueurs de réussite ou d'apparition de symptômes. Enfin, les approches individuelles basées sur l'imagerie par résonnance magnétique fonctionnelle (IRMf) utilisent cette technique pendant la stimulation active pour identifier les paramètres entraînant des modèles caractéristiques d'engagement fonctionnel associés à une réponse au traitement à long terme. Chaque méthode fournit donc des renseignements différents mais complémentaires, l'optimisation de l'efficacité d'un tel traitement nécessitant probablement une approche combinée.

Keywords: fMRI; DBS; neuromodulation; neuroimaging

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Introduction

Advances in surgical stereotaxy and neuroimaging have allowed the precise and accurate insertion of deep brain stimulation (DBS) electrodes into various intracranial targets. DBS's success relies on carefully titrated therapeutic stimulation in specific neural substrates.[1] Intraoperative targeting with millimetric accuracy is achieved through a combination of histological atlas-based stereotaxy,[2] microelectrode recordings[2] and direct target visualization on MRI.[3] Once implanted, the stimulation site can be slightly adjusted using different contacts along the electrode, and the current delivered can be titrated by way of amplitude, frequency and pulse width. Iteratively adjusting the stimulation parameters enables stimulation of only the most favorable region in terms of benefit and side effect ratio based on an individual's response to stimulation. However, making these adjustments using the currently employed empiric methods is clinically burdensome and time-consuming.[4] DBS in conditions where the effects of stimulation are delayed and advancements in DBS hardware where more parameters are adjustable further compound the unsustainable nature of this practice.[4,5] This review will discuss the imaging methods employed to better identify favorable stimulation parameters, including stimulation localization and modeling, connectome characterization and electrophysiology-guided stimulation, followed by an emphasis on how advancements in functional imaging of patient-specific responses to stimulation may improve outcomes and personalize therapy (Figure 1).

Stimulation Localization and Electric Field Modeling

Many open questions remain regarding the precise location of optimal stimulation. DBS is known to exert direct bioelectric effects on both neuronal cell bodies and axonal populations; however, the contribution of each to efficacy and side effects remains unclear.[6] Regardless, millimetric differences in stimulation appear to influence stimulation outcome.[7] Commonly the stimulation "sweet spot" is identified using group-level data by (1) determining the precise location of implanted electrodes, (2) determining the area of stimulation (volume of tissue activated: VTA) and (3) assessing the relationship with clinical outcome measures.

Several software tools have been developed for localization of implanted electrodes.[8–12] These employ various algorithms that reconstruct the desired electrode from the artifact visible on postoperative CT or MRI.[8,10,13–15] This reconstruction is then registered to the preoperative high-resolution MRI for visualization. The introduction of directional and segmented electrode (presently up to 16 channels per lead) technology has complicated this process.[16] Establishing the short-axis orientation of the electrode is required to fully utilize the directionality and steer the stimulation. Evidence suggests there is continued rotation of the electrode mainly during the first few weeks after implantation.[17] Efforts are currently being made to optimize and validate algorithms that can reconstruct this orientation from the artifact of directional markers.[17–19]

Once the electrode is localized, modeling an accurate electric field representative of the stimulation (i.e., VTA) has been a persistent challenge.[20–22] The "gold standard" for computational prediction of neurostimulation, developed in 1976, couples the electric field data to multi-compartmental neuron models; however, it is too computationally intensive for practical clinical application.[20] There have been considerable efforts spent attempting to simplify the method of calculating the spatial extent of the electric field while accounting for varying electrical stimulation parameters.[21,23–26] However, modeling how the field is influenced

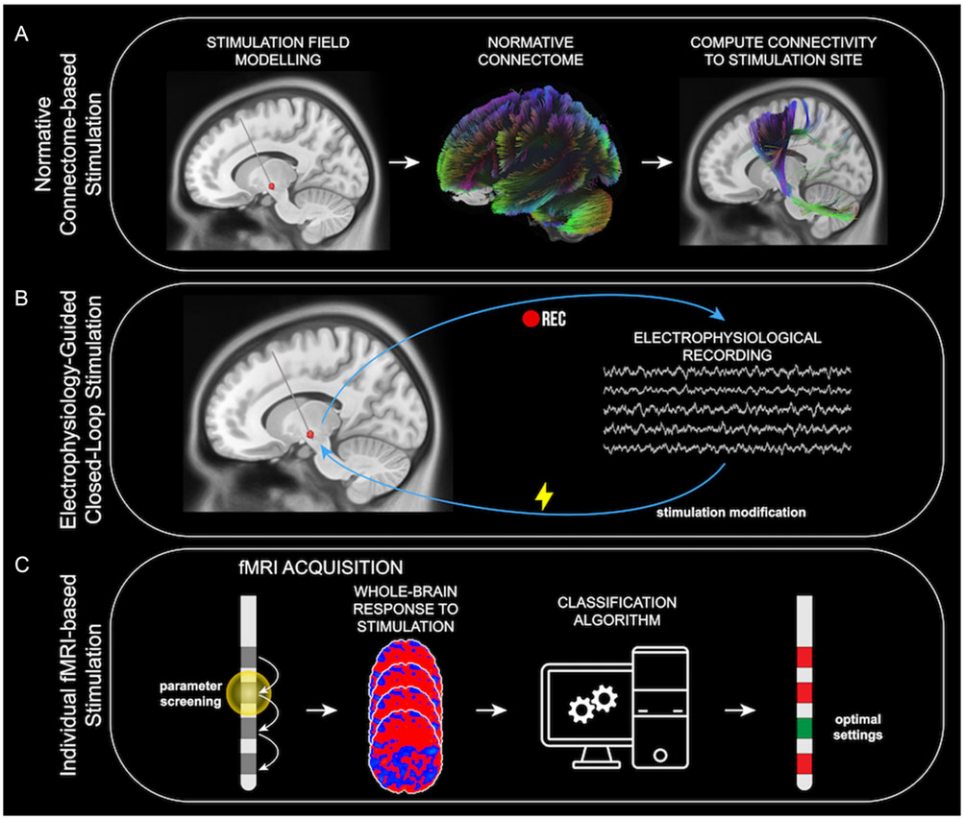

Figure 1. Imaging methods for personalizing deep brain stimulation therapy. (A) Normative connectome-base stimulation utilizes large datasets of normal or disease-matched connectivity imaging. The stimulation location for an individual patient can then be varied to engage regions associated with optimal connectivity. (B) Electrophysiology-guided closed-loop stimulation capitalizes on the electrophysiological recording capabilities of modern implanted devices to individualize stimulation parameters based on biomarkers of success or symptom onset. (C) Individual fMRI-based stimulation uses fMRI during active stimulation in various stimulation settings. Computational models link the individual imaging to whole-brain patterns of functional engagement identified as predictors of long-term treatment response to determine optimal stimulation parameters. fMRI = functional MRI.

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by surrounding tissue properties remains a considerable hurdle. Recently, finite-element modeling has been applied to neuron compartment models to manage the complexities of axonal activation during extracellular stimulation.[22] These models attempt to display a stimulation field that is relevant to the therapeutic effects of stimulation. However, the threshold of axon activation is dependent on its size.[27] Moreover, which axons are responsible for therapeutic effect is not known.[27] Furthermore, axonal polarity is determined by the potential difference between adjacent axons; thus, the entire distribution of polarity must be considered. Finally, these models fail to account for stimulation frequency, which is known to influence therapeutic effect. Simplified models are available for visualization; however, they are understood to be a limited representation of the true electrophysiology.

Together with the localization of electrodes and estimation of the VTA, retrospective group-level analyses can identify stimulation "sweet spots" associated with improved outcomes. These probabilistic maps are generated by transforming the VTA to a common space and statistically weighting the location by clinical outcome.[7,28] The resulting maps delineate zones of response in a voxelwise data-driven manner. By this method, it has been possible to pinpoint the most efficacious substrate to stimulate across large cohorts of patients and refine future targeting.[7] Direct relationships between stimulation location and clinical improvement have been established for Parkinson's disease (PD),[29–33] dystonia,[34–36] essential tremor (ET)[37–39] and obsessive-compulsive disorder,[40] among others.[7] These associations have shown some advantages in improving the efficiency of DBS programming. In the case of subthalamic nucleus (STN) stimulation in PD, effective symptom control has been associated with stimulation at contacts around the dorsolateral border of the STN.[32] Despite accurate lead placement, optimization of stimulation settings requires in-depth evaluation and individualization of each setting. Modern DBS systems with more sophisticated designs have introduced techniques to shape and steer the electric field and increase the therapeutic window but also the burden of clinical programming.[41] Several recently developed data-driven tools utilize electrode localization information to suggest stimulation settings that optimize stimulation location at the established "sweet spot."[42,43] These studies have shown improved DBS programming efficiency and non-inferior clinical results compared to standard clinician-optimized settings.[42,43]

The association between stimulation location and clinical improvement, however, must be interpreted cautiously. The VTA, in particular, remains a visual approximation of the presumed electrical field based on theoretical models and often ignores local impedance changes and intrinsic dynamics of neuronal populations.[16] Crucially, these findings lack large-scale prospective validation, and different published approaches result in a variety of different "sweet spot" localizations when used with the same data set.[28] Despite efficiency advantages, thus far, no VTA-based programming has been found to be superior to programming based on clinical grounds.

Normative Structural and Functional Connectivity

There has been a shift in focus from what is being stimulated at the local level to how stimulation exerts its effects at a network level. Accumulating evidence opposes the long-held belief that DBS exerts its effects via local modulation of the discrete gray matter nuclei in which they are implanted.[33,44–46] Instead, suggesting that modulation of distributed brain networks is at least equally important for optimal outcomes.[47,48] To appreciate the engagement of distributed brain networks, specialized MRI sequences are required. Specifically, diffusion-tensor imaging (DTI) models the structural connectivity (i.e., the white matter tracts physically connecting regions) by interpreting the diffusion of water constrained along the long axis of axons. Conversely, functional MRI (fMRI) acquired at rest measures low-frequency blood oxygen level-dependent (BOLD) signal oscillations between regions and establishes connectivity between covarying regions (i.e., functional connectivity). Both measures provide complementary, indirect information about the architecture of brain-wide networks. Through mathematical models, the networks of connected regions provide a theoretical foundation for neurobehavioral phenomena, termed connectomics.[49]

Connectomes may be studied either between individuals using patient-specific DTI or fMRI or, more commonly, using aggregate group data from large cohorts of subjects. The latter approach generates a presumed generalizable average of brain connectivity, known as the normative connectome (Figure 1A).[50] The major advantage of using a normative connectome is the high quality of the data and its flexibility of use in populations where the necessary imaging (DTI or fMRI) may not be available. This is often the case in clinical environments, where advanced imaging acquisitions are not routine, costly and often reserved for specific research scenarios. Furthermore, for rare conditions that rely on collaborative efforts for subject recruitment, comparison of images acquired using different hardware and acquisition parameters may prohibit analysis. Normative connectivity is of particular interest in DBS subjects where the acquisition of high-resolution MRI has been challenging due to safety concerns related to the implanted metallic hardware. Normative connectivity provides the means to investigate network-related questions in large, previously inaccessible groups of patients, often retrospectively.

The major shortcoming of normative connectomes is their inability to capture the subtle but important differences specific to an individual. Fundamental differences exist between the brains of healthy individuals and the brains of those affected by neurological disease.[51] For example, the sample used to define the human connectome did not include subjects older than 40 years.[52] Therefore, a connectome derived from healthy subjects may not accurately depict the disease-specific circuitopathies influencing the outcome being studied.[53,54] As a compromise, it may be advantageous to create disease-specific connectomes using scans of individuals with the same disease as the population of interest.[55] Further, matching the connectomes for other covariates, including age, sex or disease duration/severity, may improve the accuracy of findings. However, with each subdivision, the number of subjects with available images for connectome generation diminishes. It has been suggested that a minimum of 150–200 subjects is necessary for the stabilization of group connectivity estimates, thereby constraining the ability to generate disease-specific connectomes.[56] A recent PD-specific functional connectome was created from 75 subjects undergoing DBS for PD, offering an alternative to normative connectomes capable of visualizing unique differences not seen in a healthy normative connectome.[57] A few studies have directly compared the results from disease-specific and healthy control-derived connectomes with conflicting overall findings.[33,55,57–59] Larger and better-matched disease-specific connectomes will likely provide clarity.

The field of neuromodulation has leveraged normative connectomics to study networks mediating therapeutic efficacy (Figure 1A).[55] The predictive ability of normative connectivity

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profiles was investigated.[33] From the VTAs of 51 PD patients with STN stimulation, a connectivity profile was generated based on the human connectome project data (DTI and fMRI) to identify connections reliably associated with clinical motor improvement. This connectivity profile was used to predict the motor outcome of an out-of-sample cohort with 12–20% of variance explained. This concept has since been repeated for several other conditions with similar results.[40,44,60,61] Recently, small prospective studies have applied these findings in PD. Rajamani et al. developed an algorithm capable of suggesting optimal stimulation settings, which maximize engagement of tracts associated with improvement of four symptom domains (tremor, rigidity, bradykinesia and axial instability).[62] In a preliminary analysis of five patients, this algorithm was able to suggest settings with comparable symptomatic improvement compared to standard-of-care determined settings.[62] Similarly, in nine patients, Hines et al. demonstrated that prospective automated connectomic programming was safe and generated therapeutic effects similar to traditional programming strategies.[63] While promising, these studies are underpowered, and overinterpretation should be avoided.

As exemplified here, connectomes derived from large, high-quality datasets utilizing specialized MRI hardware[64,65] may be considered analogous to the anatomical reference atlases widely used in neurosurgical planning.[58,66,67] Both feature high-fidelity information insensitive to the subtleties of patient-specific anatomy. As in traditional reference atlases, normative connectomes should serve as a guide to inform patient-specific imaging.[68]

Electrophysiology-Guided Closed-Loop Stimulation

Advancements, including current steering, improved direct targeting and leveraging large normative datasets, offer the potential to enhance DBS therapy by refining the stimulation target. Despite this, PD patients still experience cognitive and speech impairment, suboptimal gait and axial motor control and residual fluctuations between on/off medication states related to stimulation.[69,70] Furthermore, limited battery life subjects these patients to subsequent exchange procedures.[71] A promising advancement to overcome these DBS drawbacks is closed-loop or adaptive DBS (aDBS), where stimulation parameters are continuously modulated based on a relevant biomarker (Figure 1B).[72] This provides the correct stimulation only when needed, lessening side effects and long-term habituation while possibly preserving battery life. A simple example of this work is position-sensitive spinal cord stimulation for pain, where the voltage is adjusted according to body position using an accelerometer.[73] So far, aDBS has been primarily studied in epilepsy using causal neural signals to change the stimulation before symptoms emerge.[74]

Adaptive DBS in PD has focused on local field potentials (LFPs) recorded from implanted electrodes (Figure 1B). The spectral power in the beta frequency range (11–30 Hz) at the STN or globus pallidus internus (GPi) has been correlated with bradykinesia and rigidity.[75–77] Averaging the beta activity over long periods allows the DBS power to be modulated based on the dynamics related to drug therapy and motor on-off states, leading to a reduction in battery usage by ~ 50% and a reduction in on-state dyskinesias.[78] Conversely, capturing the bursting nature of spontaneous beta activity can identify states of severe bradykinesia and rigidity.[79] Using the beta signal to trigger or increase stimulation to terminate the pathological signal has achieved a 50% reduction in power requirements and a reduction in adverse effects on speech compared to conventional continuous stimulation.[75,80,81] Better control of bradykinesia and rigidity has also been reported with beta signal-based aDBS.[76] The arrival of commercially available DBS devices with simultaneous neural sensing and stimulation capabilities has enabled wide-scale study of aDBS in chronically implanted patients.[82,83] Opportunities to develop more sophisticated aDBS approaches using machine learning based on the precise correlation between long-term electrophysiological signal recording and symptom severity are arising across a variety of diseases.

Importantly, LFP-based open-loop programming is already largely adopted due to the availability of DBS devices able to wirelessly stream from the brain (Medtronic Percept PC and RC, Dublin, Ireland). Multiple lines of evidence have confirmed that stimulating at the contact with the strongest LFP (e.g., beta in PD, alpha in ET) is associated with the best outcome. Likewise, the reduction of LFP with ongoing stimulation can be used to confirm the proper contact selection and identify the amount of stimulation needed to obtain such benefit.[76] This latter approach is particularly favorable in conditions with a delayed clinical effect of stimulation, such as dystonia.[5] Notably, the same device is capable of closed-loop stimulation using three different control algorithms: single threshold, single inverse threshold and dual threshold. The closed-loop capability is presently available only in Japan until approval from other health authorities is granted.

Individual Functional Response to Stimulation

As our understanding of the mechanism of DBS grows deeper, it is clear that although stimulation acts on the local region around the electrode, the therapeutic effects and side effects that manifest are the result of brain-wide network engagement.[47,48] As discussed, this engagement may be investigated using the connectivity of the stimulation site to the rest of the brain using normative connectomes.[50] Although applicable to large groups of varied data, this method is limited by assumptions that patient-specific circuitopathies are accurately represented by normative data,[51,84] registration and localization errors of estimated VTAs are minimal,[85–88] and the modeling of electrical stimulation is a representation of true electrophysiology.[16] Conversely, the acquisition of neuroimaging data demonstrating an individual's response to stimulation has provided key insights into the mechanism of DBS and has potential clinical application as a personalized biomarker for stimulation success.[89,90]

Early work

In PD, aberrant and dysfunctional processing within the cortico-striato-thalamo-cortical (CSTC) circuit has been hypothesized to play a key role in pathophysiology.[91] Using molecular neuroimaging, in particular positron emission tomography (PET), this spatial pattern of abnormal activity has been uncovered.[92,93] The expression of this pattern is increased as the disease progresses and decreases with treatment, including pharmacotherapy and DBS.[92,93] This work has also been extended to study the acute effects of active DBS on whole-brain metabolism.[89] Acute stimulation reproducibly engaged the CSTC circuit, leading to increases in activity in the STN, thalamus and pallidum.[89] This is consistent with increased afferent inhibitory pallidothalamic tract activity as a proposed therapeutic mechanism.[94,95] Molecular neuroimaging studies such as these represent a final common output of complex neurochemical and molecular mechanisms and a surrogate for direct synaptic activity.

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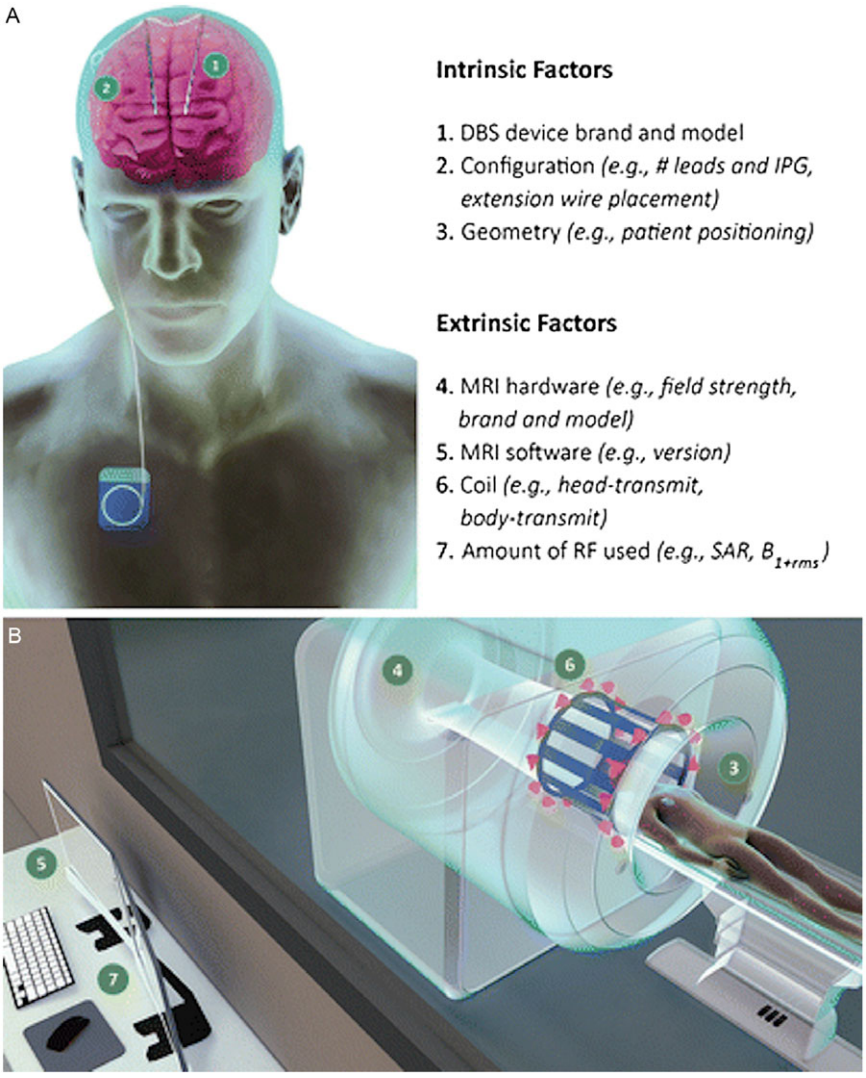

Figure 2. Summary of risk factors contributing to DBS device heating. Intrinsic and extrinsic risk factors are listed and labeled on a depiction of an implanted DBS device (A) and an illustration of an MRI suite (B). B_{1+RMS} = root-mean-square value of MRI effective component of RF magnetic (B_1) field; IPG = implantable pulse generator; RF = radiofrequency; SAR = specific absorption rate. Reproduced with permission from Boutet et al. Radiology 2020.[102]

While molecular neuroimaging has advantages in studying a specific substrate, high-resolution fMRI may investigate changes in brain circuitry with superior spatial-temporal resolution. Approaching the end of the twentieth century, there had been no reports of fMRI studies in patients with implanted DBS electrodes.[96] Although already used routinely in other clinical situations, hesitation with proceeding in DBS patients was related to the potential risk of injury caused by displacement or heating of the implanted electrodes.[96–99] Owing to early in-human work and phantom studies establishing the safe acquisition parameters, fMRI in patients with implanted and active DBS could be performed, ushering in a new era of neuroimaging investigations into the effects of DBS.

The pioneering work in PD by Jech et al. occurred in 2001. Here, they reveal acute motor circuit engagement using fMRI during active STN stimulation.[100] Their findings align with PET studies demonstrating ipsilateral activation of the GPi and ipsilateral ventrolateral thalamus.[100] In addition to local effects, remote effects in the ipsilateral dorsolateral prefrontal cortex were witnessed, suggesting a mechanism beyond long-lasting depolarization mimicking a lesional effect.[100] Complementing this, early investigations also showed that these effects were specific to the site stimulated and circuit engaged. Stefurak et al. showed motor cortex, ventrolateral thalamus and cerebellar activity changes with STN stimulation.[101] However, stimulation marginally superior and lateral into the fields of Forel showed more prominent engagement of the prefrontal cortex, anterior cingulate and anterior thalamus associated clinically with reproducible acute depressive dysphoria.[101] These early findings showcased the role of fMRI in probing the mechanism of DBS, revealing the feasibility of studying the acute local and remote effects of stimulation with sensitivity to the stimulation site and disease condition. Excitement in this technique came to an abrupt halt in the subsequent years when several MR-related adverse events were reported.[102] This necessitated a reevaluation of the safety of MRI in this population.

MR-related adverse events and safety implications

MRI scanning of implanted metallic DBS systems is subject to stringent safety guidelines, which have restricted its use.[103] In 2009, it was reported that close to 50% of centers surveyed did not use MRI in patients with implanted DBS.[104] MRI restrictionsss arise from safety concerns mainly related to the potential for radiofrequency (RF) induced heating of the metallic hardware during the scanning (Figure 2).[96–99]

There are five reports of injury involving RF currents in the DBS literature, three of which are MR-related.[102] This prompted the US Food and Drug Administration (FDA) to issue a warning

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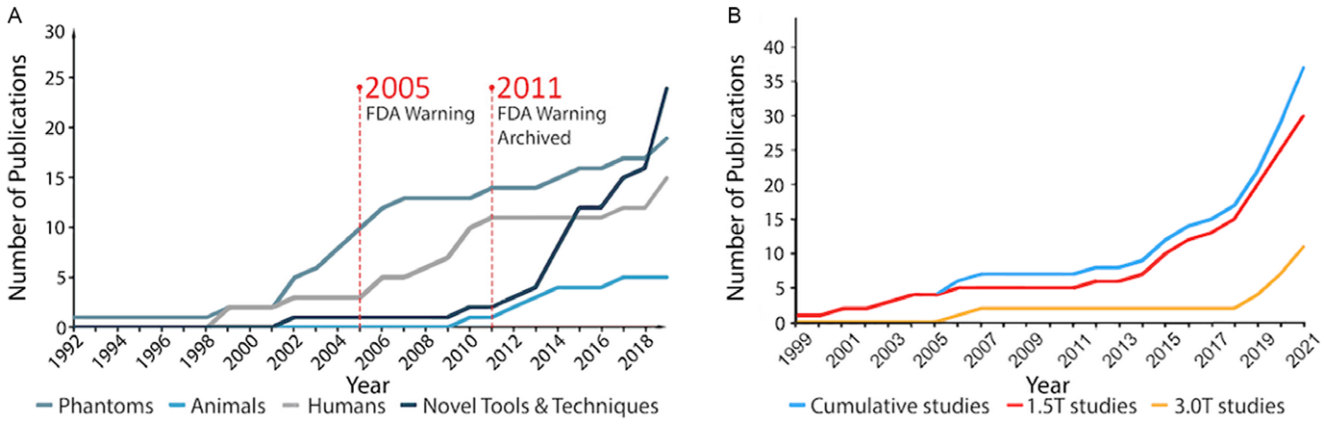

Figure 3. Graphs depicting MRI-DBS-related publication over time. (A) A line graph representing the cumulative number of DBS-related MRI safety studies published from 1992 to 2019. The studies were categorized into phantom, animal, human and technique safety studies. Modified with permission from Boutet et al. Radiology 2020.[102] (B) A line graph representing DBS-fMRI studies over time. The rate of publication increasing, particularly in the last 5 years. Modified with permission from Loh et al. Brain Stim. 2022.[118] DBS = deep brain stimulation; FDA = Food and Drug Administration; fMRI = functional MRI; T = tesla.

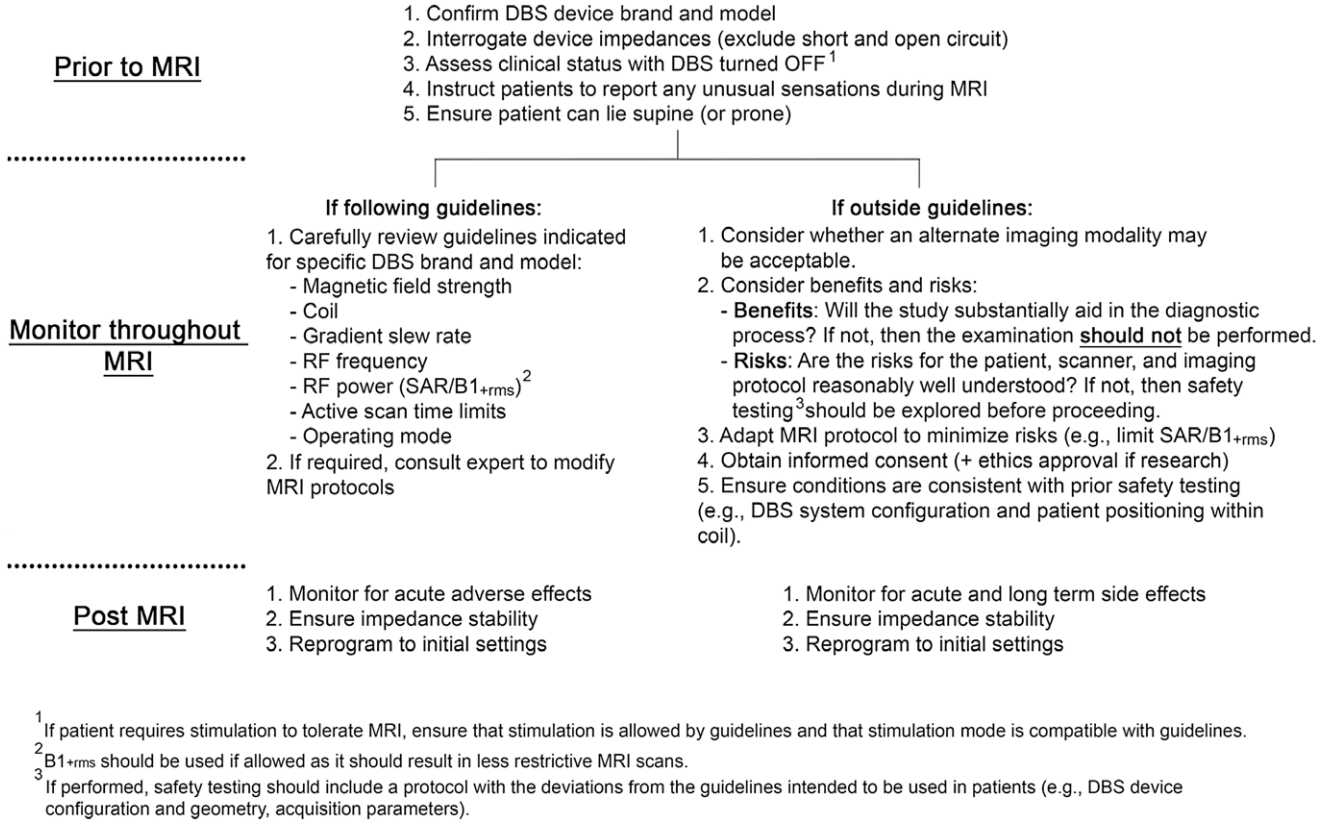

Figure 4. Summary recommendations of best practices for MRI in patients with DBS devices. These recommendations are based on guidelines from DBS vendors, reviewed literature and institutional experience. B_{1+RMS} = root-mean-square value of MRI effective component of RF magnetic (B_1) field; DBS = deep brain stimulation; RF = radiofrequency; SAR = specific absorption rate. Reproduced with permission from Boutet et al. Radiology 2020.[102]

regarding the MR imaging of patients with DBS devices in 2005 (Figure 3A).[97] This led to strict vendor guidelines including restricting the field strengths (e.g., 1.5T) and limiting parameters related to the amount of RF being delivered (e.g., specific absorption rate [SAR], root-mean-square value of the MRI effective component of the RF magnetic [B_1] field [B1+rms]). Between 2005 and 2011, several human studies aimed to confirm the safety of the FDA guidelines, with no adverse events reported in over 3000 DBS patients scanned at 1.5T (Figure 3A).[104] As discussed above, there is considerable interest in investigating DBS patients outside of these restrictive guidelines, including using fMRI during active stimulation. As a result, recent studies in phantoms have examined the safety of these systems outside vendor guidelines, reporting acceptable temperature rises under local experimental conditions (Figure 3A).[98,105–110] This was further expanded in vivo in a publication where 102 subjects with fully internalized DBS were scanned with 3T structural T1-weighted and fMRI outside vendor guidelines, confirming

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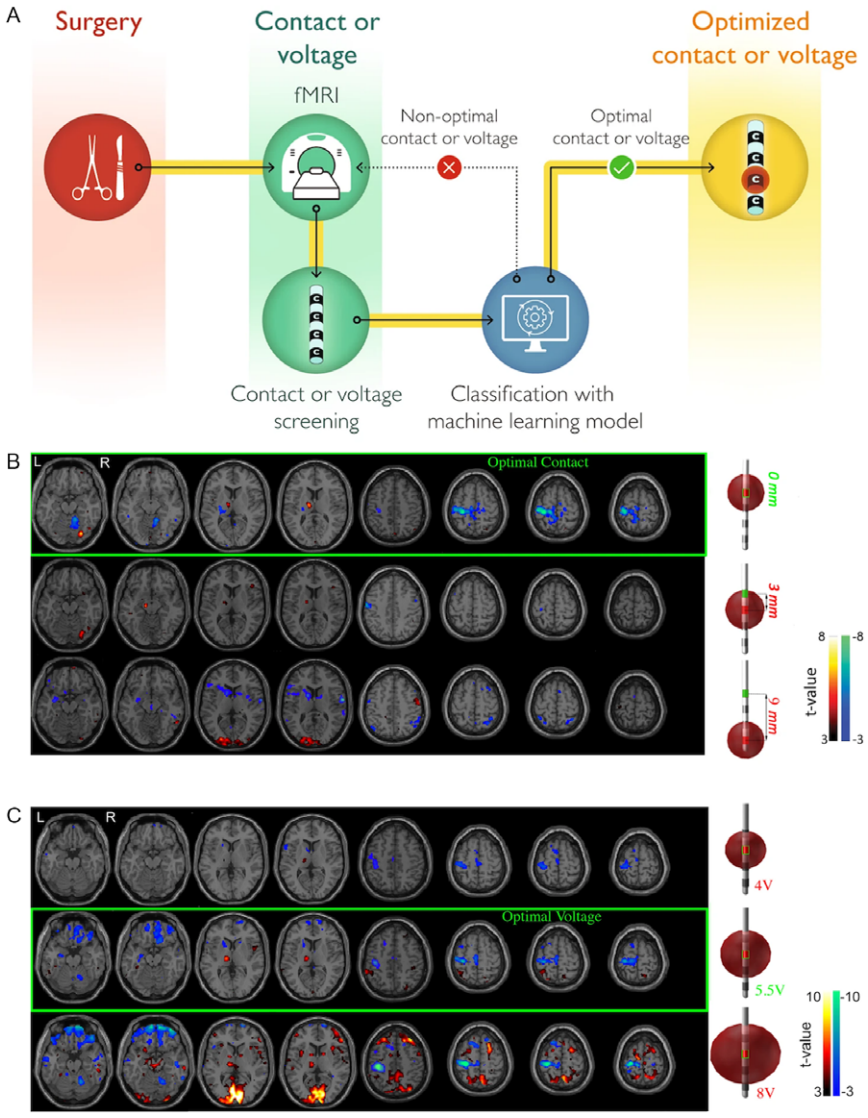

Figure 5. (A) Experimental design for postoperative DBS contact and voltage screening using fMRI. fMRI is acquired on each contact and a range of clinically relevant voltages. The resulting images are analyzed using a machine learning classification model, and the most optimal settings tested are identified. The model identifies a pattern of network engagement specific to stimulation at the clinically optimized contact (visualized in panel B) and voltage (visualized in panel C). DBS = deep brain stimulation; fMRI = functional MRI. Modified with permission from Boutet et al. Nat. Comm. 2021.[90]

safety.[111] Importantly, these findings may not be generalizable to different MRI or DBS systems, and local institutional safety testing should be performed until generalizability can be confirmed.[112,113]

Advancements in DBS hardware and neuroimaging techniques have partially overcome the challenges of performing MRI in patients with implanted and active DBS systems. However, heat at the electrode tips remains the primary risk associated with DBS devices. Electrode and device designs incorporating components to act as heat sinks and improve insulation have been studied.[114,115] Other studies report modification to RF coils, resulting in lower SAR and heating and custom MRI acquisition parameters to limit the use of RF pulses.[102] The progressive development in this field has led to the evolution of vendor guidelines and considerable growth in the number of publications (Figure 3B).[102] Select modern DBS devices have been deemed conditional at 3T and for whole-body scanning.[102] When imaging outside of published guidelines, emphasis should be placed on minimizing SAR and B1+rms.[102] The current best practice guidelines based on DBS vendor recommendations, reviewed literature and institutional experience are summarized in Figure 4.

A modern era of functional imaging in response to DBS

Improved understanding of MRI-DBS safety has facilitated a growing number of studies utilizing fMRI to provide unique mechanistic and therapeutic insights.[106,110,111,116,117] As of 2022, there were 37 studies investigating fMRI during active DBS, with over half published within the last 5 years (Figure 3B).[118] The majority of these studies focused on STN-DBS in PD; perhaps more notable was the paucity of GPi-DBS studies.[118] Encouragingly, emerging and experimental indications for DBS are represented in fMRI-DBS studies, reflecting the utility for characterizing the effects of stimulation, refining patient selection and targeting.[118] These studies have demonstrated the large-scale networks modulated by DBS and the variation in stimulation-evoked response related to the stimulation site, stimulation parameters, patient characteristics and degree of treatment efficacy.[118] Reviewing this literature suggests a movement beyond characterizing just the brain response to stimulation but increasingly making associations between these responses and clinical outcomes.[118] This hints at the translational potential of fMRI in DBS, particularly in identifying biomarkers of therapeutic success. As discussed, the process of stimulation parameter optimization is burdensome and

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especially difficult in instances with delayed clinical feedback, such as dystonia, depression and Alzheimer's disease.[4,5] fMRI during active DBS appears to be an accessible and rapidly acquired objective marker with the potential to guide programming (Figure 1C).[90] Furthermore, the fMRI response to DBS has been correlated with long-term motor improvement, suggesting intraoperative fMRI may help refine electrode placement.

A study using a large cohort of PD-DBS patients found that fMRI acquired prospectively at 3T demonstrated a characteristic pattern of brain response to clinically optimal stimulation.[90] Specifically, over 200 fMRI sessions were conducted in 67 PD-DBS patients during active cycling stimulation. The sessions were acquired in both clinically optimal and nonoptimal settings by adjusting the contact and amplitude (Figure 5). Comparing the stimulation-dependent functional response obtained during these sessions allowed the training and validation of a machine learning classification model able to identify optimal stimulation settings with a 76% out-of-sample testing accuracy.[90] This model relies on features within 16 regions throughout the brain, one of the more prominent being the decrease in stimulation-dependent BOLD signal in the ipsilateral primary motor cortex in addition to thalamic and cerebellar changes observed (Figure 5). These findings, central to the classification model, are consistent with previously reported imaging and electrophysiological work.[100,118–124] At the network level, it appears that both DBS and levodopa attempt to normalize the PD-related spatial covariance pattern.[125,126] Interestingly, inspecting the pattern of engagement from nonoptimal stimulation shows the involvement of non-motor circuits, including the visual cortices and operculum.[90] This is likely a manifestation of target-adjacent stimulation. As the location of stimulation moves away from the dorsolateral STN, surrounding white matter tracts and associative/limbic territories of the STN may be recruited.[61,127,128] These consistent neuroimaging findings suggest a common neuroanatomical network mediating therapeutic improvement, and engagement outside of this network possibly explains the presence of adverse events.

A central finding in fMRI studies during active DBS is that changes to stimulation (e.g., cycling the device on/off) will manifest in rapid fMRI responses, preceding changes in symptoms that may take hours/days to reappear.[90,129–133] These studies have further shown an association between acute stimulation-dependent activity and long-term clinical outcome, an association robust enough to build predictive models of outcome.[90,129,130] These desirable features position fMRI as a biomarker of stimulation success. As hinted at earlier, these biomarkers are considered increasingly important in the expanding parameter space of modern DBS devices. The trial-and-error testing of individual parameters is not sustainable. Within the constraints of short clinical visits, optimization is particularly challenging when clinical features lack immediate feedback. The current literature suggests it is conceivable that contact and amplitude settings could be efficiently optimized using fMRI.[90] Beyond this, the fMRI signal appears to be specific to individual diseases and stimulation targets, showing unique patterns with predictive capability in GPi-DBS for dystonia,[130] subcallosal cingulate DBS for depression,[129] ventral striatum DBS for obsessive-compulsive disorder[134], the anterior thalamic nucleus for epilepsy[135] and the ventrocaudalis nucleus for pain.[96] These conditions require days to weeks between setting changes for a visible clinical response.[5]

Future directions

The landscape of MRI in the context of implanted DBS and particularly fMRI during active stimulation has progressed considerably over the past two decades. Acquisition of large-volume, high-quality data remains a challenge, and safety concerns loom in the forefront. Although our knowledge of MRI safety continues to grow and the data demonstrating safe acquisition are increasing, there is still a lack of standardization in MR hardware, DBS hardware, acquisition parameters and implanted DBS configurations. This requires that institutional safety testing be performed prior to any scanning outside of device manufacturer guidelines. However, manufacturers are developing DBS hardware with materials and insulation that are expected to become MR compatible regardless of configuration and at increasing field strength.

One of the main emerging utilities of fMRI in DBS is as a rapidly acquired, objective biomarker of stimulation success. Although initial studies suggest it may simplify and accelerate the DBS optimization process, prospective validation of these models is still required.[90] In an effort to facilitate the acquisition of this data, work is underway developing more advanced modeling capable of real-time processing during acquisition and actively informing the fMRI sampling strategy by predicting likely beneficial parameters to trial.[136] Most studies identify fMRI patterns of response associated with global outcome improvement. fMRI may afford the granularity to reveal networks mediating individual symptom effects due to the robustness of the signal and specificity between diseases. The field would benefit from further dissection of these stimulation-dependent responses and prospective clinical validation.

More work will need to be done to lessen the artifact of the lead as seen at the MRI and to identify the exact lead orientation. Not surprisingly, a recent double-blind cross-over study compared standard programming, neuroimaging-based programming (VTA on a commercialized software) and LFP-based open-loop programming in PD treated with STN. Patients were asked to judge the best programming parameters, and only one out of eight subjects favored the neuroimaging-based one.[137]

Competing simultaneous imaging and DBS modalities

Although there are significant advantages of fMRI in terms of spatial resolution, accessibility and robustness of response, there remain pervasive safety limitations. Concurrent with the study of fMRI responses to stimulation, several other modalities have investigated DBS-evoked responses, including electroencephalography (EEG) and magnetoencephalography (MEG). Electrophysiological recording of response to stimulation has long been investigated.[138–141] Here, similar to fMRI, the cortical response to stimulation is measured and time-locked to independent and individual DBS pulses. While capable of measuring sub-second changes in neuronal activity, EEG is limited by spatial resolution, high-frequency artifact related to clinically relevant DBS settings and poor sensitivity to low amplitude electrophysiological changes.[142–145] Despite these limitations, recent studies using EEG have observed that cortical evoked potential amplitudes over the motor cortex and supplementary motor area are associated with therapeutic efficacy.[146–148] Conversely, MEG localizes neural activity on the order of milliseconds by detecting the magnetic fields generated by neural currents.[149,150] It can noninvasively and reliably

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sample the entire cortical envelope and detect clinically relevant higher-frequency electromagnetic oscillations, which are typically too low in amplitude for EEG to detect.[151] Only recently, however, has MEG been available to study patients with implanted DBS electrodes. DBS-generated artifacts have previously obscured data collection, but several groups have worked to resolve this by employing artifact removal algorithms.[152,153] Spatial and temporal patterns of DBS-evoked MEG response are actively being investigated to identify additional biomarkers of stimulation success. Once robust and reproducible electro-/magnetophysiological patterns of evoked response are identified, the logical next step will be clinical application as a personalized programming approach. Until then, these modalities require further data acquisition and outcome definition.

Conclusions

Three emerging methods of personalizing DBS programming are discussed here (Figure 1): normative connectomic work, which incorporates stimulation localization information and large normative datasets; electrophysiology-guided stimulation, which is responsive to local changes in neuronal oscillation and firing rate; and finally, fMRI, which provides insight into the whole-brain response to stimulation. Each method provides different but complementary information, and maximizing treatment efficacy likely requires a combined approach. One suggested approach may be to begin by stimulating the precise location based on normative connectomics followed by parameter adjustment based on whole-brain engagement on fMRI and ongoing fine-tuning using responsive electrophysiology. Determining the precise role in clinical practice will require prospective validation. There are currently no studies that assess the utility of these biomarkers to guide DBS programming.

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