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Deep brain stimulation think tank: Updates in neurotechnology and neuromodulation, volume IV

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Deep brain stimulation think tank: Updates in neurotechnology and neuromodulation, volume IV

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Editorial: Deep brain stimulation think tank: updates in neurotechnology and neuromodulation, volume IV

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Editorial on the Research Topic
Deep brain stimulation think tank: updates in neurotechnology and neuromodulation, volume IV

Deep brain stimulation (DBS) is a rapidly advancing field being shaped by emerging research and techniques that are enabling increased understanding of brain anatomy and physiology, the pathology of neurological and psychiatric disorders, and viable capabilities and roles of neuromodulation therapies. Since 2012, the DBS Think Tank has been an annual venue for multidisciplinary experts to interactively address challenges, advancements, and opportunities in the field. Convening clinicians, researchers, engineers, ethicists, and industry professionals, the DBS Think Tank has addressed ways of improving clinical outcomes; technological innovations; neurophysiological and imaging-based markers of pathology and response to DBS; emerging indications and targets for DBS; advancements in commercial devices and technologies; and ethical challenges and their potential solutions.

As a vector for disseminating information and with support from the Frontiers Editorial Office, this Research Topic has been developed to focus on topics presented at each year's DBS Think Tank. The proceedings summarizing the annual meetings have also been consistently published as part of this Research Topic, including the recent meetings in 2022 (Wong et al.) and 2023 (Johnson et al.) in the present volume.

In this editorial, we summarize the sixteen studies presented in the fourth volume, which address: (1) improving clinical practice; (2) neuroimaging techniques to optimize DBS targeting; (3) generating deepened insights into the effects of DBS on pathologic symptoms; (4) utility of DBS to treat certain neuropsychiatric disorders; and (5) patient-focused considerations for translational research.

Improving clinical practice and technology translation

Although DBS is regarded as a primary surgical therapy for Parkinson's disease (PD), access to DBS remains relatively limited. Memon et al. performed a systematic review to evaluate the influence of demographic and socioeconomic factors on patient access to DBS. Their investigation revealed that individuals who were elderly, female, Black, and from low socioeconomic backgrounds and developing countries encountered greater obstacles in accessing DBS for PD. Considering these findings, the authors suggest that strategies engaging all stakeholders to reduce such disparities should be developed and implemented.

DBS is a treatment option for essential tremor (ET); however, the effects of DBS on cognitive outcomes in ET are not well characterized. Al Ali et al. reviewed the existing literature to evaluate whether DBS targeting the ventral intermediate nucleus (VIM) or caudal zona incerta/posterior subthalamic area (cZi/PSA) induced cognitive changes. Their analysis found that measures of verbal cognitive ability declined in some ET patients treated with DBS; however, these changes were not significant, and severe decline was relatively rare. Controlled trials are needed to thoroughly investigate the contributing factors.

Case reports are valuable for sharing challenges associated with DBS and potential clinical indications. Holland et al. reported a patient who received DBS for PD, whereafter a pocket hematoma formed around the implanted pulse generator (IPG), which led to behaviors resembling "Twiddler's syndrome" (i.e., flipping the device within the pocket) and ultimately led to device failure. To prevent this complication, the authors suggested anchoring the IPG to a deep fascial layer or using an antimicrobial pouch.

MacLean et al. reported three patients with childhood-onset dystonia whose axial or orofacial symptoms were refractory to standard pallidal DBS and subsequently underwent DBS targeted to the pedunculopontine nucleus (PPN). All of the patients had clinically significant dystonia improvement but required intensive DBS programming over several months. This case series suggests the PPN may be a potential DBS target for patients from this subpopulation, but larger controlled studies are required for thorough investigation.

Imaging to optimize stimulation targeting

Imaging is crucial for DBS targeting and understanding the effects of DBS on local neuroanatomy and brain networks. Emerging techniques aim to identify neuroanatomical structures that are not easily delineated in structural MRI. Patriat et al. introduced the novel method of diffusion MRI for anatomical nuclei imaging (DiMANI) to visualize thalamic nuclei in individual patients. DiMANI showed high reproducibility and clinical relevance and thus could refine thalamic DBS targeting approaches.

Computational models of DBS complement imaging by estimating the effects of DBS on local neural structures and networks. Patrick et al. comprehensively reviewed the methods and applications of modeling the volume of tissue activated (VTA) by DBS. The authors compared various VTA methods, parameters, and software platforms available for integrating imaging and computational modeling. Their review can serve as a central resource for clinicians and researchers incorporating imaging and VTA methods.

Imaging and computational models of DBS were employed by Yu et al. to investigate whether DBS targeting should be tailored to ET vs. "ET-plus," defined as ET and additional neurologic signs, such as impaired gait and dystonic posturing. The authors found no significant differences in the optimal stimulation site or VTA-fiber pathway overlap between groups. However, objective methods to discern ET and ET-plus are needed, and other markers (e.g., electrophysiology) could be valuable to refine DBS methods for distinct patient populations.

Unraveling the effects of DBS on pathologic symptoms

Major research foci have been on understanding the pathophysiological basis of neurological and neuropsychiatric symptoms and how DBS modulates these symptoms. Munoz et al. studied the effects of subthalamic nucleus (STN) DBS and levodopa medication on eye and limb movements in PD patients using a visually-guided reaching task administered either on/off medications or on/off STN DBS. Levodopa medication worsened visual saccade performance but improved reaching performance, while STN DBS improved both saccade and reaching performance. These findings highlight the importance of evaluating multiple measures when assessing the effects of particular treatments on PD disease state.

Non-motor symptoms of PD are becoming increasingly relevant to DBS therapy. Memon et al. employed EEG-monitored sleep to study the effects of low (60 Hz) and high (≥130 Hz) frequency STN DBS in PD patients with self-reported sleep complaints. Sleep spindle density was significantly higher with high-frequency DBS compared to low-frequency DBS, whereas slow wave activity during non-rapid eye movement (NREM) sleep was increased during low-frequency DBS compared to high-frequency or off DBS. Their findings motivate research toward developing more precise DBS parameters for positive effects on sleep.

Advancing DBS in neuropsychiatric disorders

Neuropsychiatric symptoms can be a debilitating non-motor component of PD. Muhammad et al. studied the effects of STN DBS on evaluating emotional stimuli in individuals with PD. Subjects participated in emotional picture-viewing tasks while STN local field potentials (LFP) and EEG were recorded. Negative emotionally valent pictures were associated with time-locked, acute STN DBS. With 130 Hz DBS, alpha power decreased in response to negative vs. neutral images irrespective of stimulation. However, with 10 Hz DBS, alpha power was not decreased, but power in the alpha and beta bands

were increased. Therefore, low-frequency DBS may synchronize neurophysiological activity, which could potentially guide new DBS paradigms for neuropsychiatric symptoms.

DBS appears promising for treating specific treatment-resistant neuropsychiatric disorders, such as treatment-resistant depression (TRD) and obsessive-compulsive disorder (OCD). Allawala et al. studied the effects of stimulation in the subcallosal cingulate (SCC) or ventral capsule/ventral striatum (VC/VS) on prefrontal neural activity measured with stereo-EEG in two subjects enrolled in an ongoing clinical trial investigating DBS for TRD. DBS in the SCC vs. the VC/VS differentially modulated gamma band activity but in a shared prefrontal circuit. Their findings may provide preliminary evidence of brain networks involved in the therapeutic effects of DBS for TRD.

Studies of DBS in OCD have begun transitioning toward network-guided approaches. Basich-Pease et al. reported a patient who underwent bilateral anterior limb of the internal capsule (ALIC) DBS for the treatment of OCD and TRD. The patient experienced initial modest improvements, but their right lead was not contributing, potentially due to a suboptimal location. Lead repositioning was guided by tractography to target fiber pathways connecting the medial and ventrolateral prefrontal cortices and mediodorsal thalamus. After lead repositioning, the patient's OCD symptoms and subjectively reported quality of life substantially improved. This case highlights the value of tractography in evaluating and guiding DBS electrode targeting and repositioning.

Patient-focused considerations for translational research

Commercial DBS devices that support chronic recordings have opened new opportunities for studying biomarkers of symptoms and behavior, especially in the naturalistic environment. Feldmann et al. present a patient engagement study for chronic DBS research focused on capturing patients' perspectives on study design, data acquisition, and infrastructure. Involving patients' perspectives in these dimensions of research will be important for defining and implementing strategies to positively affect patient motivation, participation, and compliance.

Identifying biomarkers of symptoms is important for developing patient-focused DBS approaches. Using such biomarkers, adaptive DBS (aDBS) methods can be employed to titrate stimulation in real time according to the patient's symptoms. Wilkins et al. outline key considerations for successfully implementing aDBS, including identifying reliably detected biomarkers and selecting parameters to optimize algorithm performance to meet patients' needs. These considerations are critical to ensure the successful translation of aDBS to clinical applications.

Conclusions

The studies presented in this volume provide a broad view of the current innovations, challenges, and opportunities of DBS. Iterative advancements in neuroimaging, computational modeling, and electrophysiological techniques have deepened our understanding of the pathophysiology of various neurological and neuropsychiatric disorders and refined targets for DBS to achieve beneficial therapeutic effects. The overarching goal is to translate cutting-edge technology toward developing more efficient and effective DBS approaches. However, challenges remain that impede widespread clinical adoption and employment of DBS, including disparities in access to DBS in underserved populations and in patients with less common disorders who do not have other effective treatment options. Improving the technologies, guidelines, and policies that enable more facile use of DBS will require multidisciplinary collaborations among clinicians, researchers, engineers, ethicists, industry professionals, policymakers, and patients. The DBS Think Tank aims to engage national and international colleagues by providing a venue and resource for current and future collaborations in the field.

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Proceedings of the 10th annual deep brain stimulation think tank: Advances in cutting edge technologies, artificial intelligence, neuromodulation, neuroethics, interventional psychiatry, and women in neuromodulation

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The deep brain stimulation (DBS) Think Tank X was held on August 17–19, 2022 in Orlando FL. The session organizers and moderators were all women with the theme *women in neuromodulation*. Dr. Helen Mayberg from Mt. Sinai, NY was the keynote speaker. She discussed milestones and her experiences in developing depression DBS. The DBS Think Tank was founded in 2012 and provides an open platform where clinicians, engineers and researchers (from industry and academia) can freely discuss current and emerging DBS technologies as well as the logistical and ethical issues facing the field. The consensus among the DBS Think Tank X speakers was that DBS has continued to expand in scope however several indications have reached the "trough of disillusionment." DBS for depression was considered as "re-emerging" and approaching a slope of enlightenment. DBS for depression will soon re-enter clinical trials. The group estimated that globally more than 244,000 DBS devices have been implanted for neurological and neuropsychiatric disorders. This year's meeting was focused on advances in the following areas: neuromodulation in Europe, Asia, and Australia; cutting-edge technologies, closed loop DBS, DBS tele-health, neuroethics, lesion therapy, interventional psychiatry, and adaptive DBS.

KEYWORDS

deep brain stimulation (DBS), artificial intelligence, neuroethics, Parkinson's disease, dystonia, interventional psychiatry, adaptive DBS, epilepsy

Introduction

The 10th annual DBS Think Tank had a theme of *women leaders in neuromodulation* and Dr. Helen Mayberg was the invited keynote speaker. In her talk, Dr. Mayberg emphasized that the DBS field needs hedgehogs, foxes, and chimera. Hedgehogs are useful because of their deep knowledge. This knowledge is more than knowing the rules and cases. It is knowing how all the pieces fit together. Foxes are useful, because they have perspective. Foxes can see the forest and how the trees fit together. Finally, chimera are useful because they can bring together hedgehogs and foxes into effective teams. She emphasized that her mentor taught her to find a problem you care about and to focus on studying a disease and not a method. Her mentor stressed that "methods change." Dr. Mayberg illustrated how hedgehogs, foxes and chimera need to interact with each other in the pursuit of science using her own experiences over the past three decades asking questions about sadness and depression. Starting with sadness, she and her team developed imaging, biomarkers and treatments, all based on understanding the underpinnings for the network underlying depression (**Figure 1**). This work led to a series of pilot studies which contributed to refinement of the DBS target for depression. Her studies informed the reasons for the shortcomings of the recent industry based clinical trials of DBS for depression. Collectively, the science has driven a refined approach for depression DBS, which will soon re-enter large scale clinical trials. As there are several budding and emerging disciplines within the field of DBS, Dr. Mayberg advises that this team-based approach with core role players is key to successfully exploring the science.

Bench therapies inspiring neuromodulation

Neuromodulation therapies have been largely developed using a human intra-operative and post-operative learning approach. In the last decade, however, there has been an explosion in bench neuromodulation-based research. Terms like "optogenetically inspired DBS" have recently emerged and there has been a greater focus on "mechanism of action" and development of animal models of DBS (Vedam-Mai et al., 2021). Animal models of DBS have driven a re-birth of a variety of DBS targets such as cerebellar DBS.

Optimizing DBS using physiologic signals and biophysical modeling

Programming optimization remains a critical clinical challenge that continues to hamper efficient and widespread use of deep brain stimulation (DBS) therapy. Automated programming using closed-loop paradigms has been an exciting and important next step in the development of next generation DBS therapy. Control signals for using with automated programming strategies can be obtained from kinematic (e.g., accelerometer, gyroscope), electrophysiologic (e.g., evoked potentials, beta power), and/or imaging (e.g., patient-specific activation models) domains. These strategies can provide quantifiable metrics for disease or symptom severity, treatment efficacy, target engagement, and side effect severity. Automated programming for

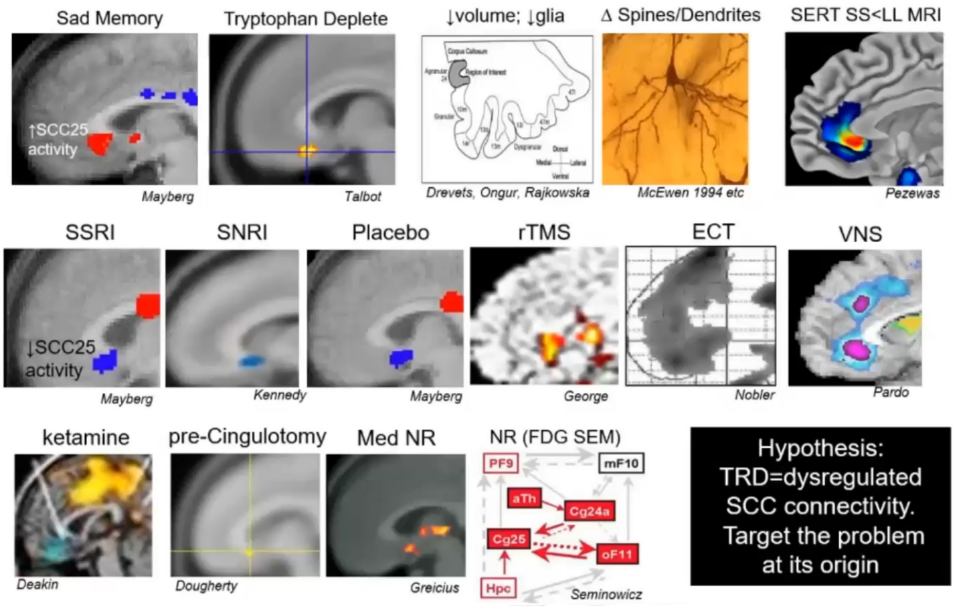

FIGURE 1
Understanding where sadness is—This figure illustrates various neuroanatomical localizations of key nodes related to depression as a psychological state, the pharmacological treatment of depression, neuromodulation of depression, and recovery from depression. Through a series of small experiments, this collective information has built a network that identified connectivity to the SCC as a critical player in treatment resistant depression. MDD, major depressive disorder; TRD, treatment resistant depression; SCC, subcallosal cingulate.

tremor suppression in patients with Parkinson's disease (PD) and essential tremor has also been successfully implemented and piloted using kinematic signals (Haddock et al., 2018; Sarikhani et al., 2022). Bayesian optimization with safety constraints has further enabled safe and efficient programming with comparable tremor outcomes when compared to programming that is performed by expert clinicians (Sarikhani et al., 2022). Image-guided programming aims to use patient-specific computational DBS activation models to choose stimulation settings in order to maximize computationally predicted stimulation effects in the target region and to avoid side-effects. Computational DBS activation models should be systematically validated to assure that predictions are sufficiently accurate to be reliably useful and applicable in clinical practice. This outcome can be potentially accomplished by comparing *in vivo* electrophysiologic measures of pathway activations with model predictions from the same set of subjects (Miocinovic et al., 2018; Howell et al., 2021). Model performance is critically dependent on accurate lead localization and appropriate selection of pathway excitability. Model accuracy will perform better for omnidirectional rather than directional settings. Further model development will help to resolve these issues for the field (Howell et al., 2021).

Contribution of non-human primate model to DBS therapy

Non-human primate (NHP) models can be a useful tool in the discovery and improvement of DBS therapy. DBS can possibly reduce the frequency and severity of seizures, however few patients convert to seizure freedom. The NHP model of penicillin-induced seizures is an "on-demand model" for focal seizures (cortical and temporal lobe) that can be used to characterize the anatomically relevant pathways involved in seizure propagation and to identify critical nodes for DBS intervention. Dr. Devergnas used this model to study the involvement of the basal ganglia in the control of cortical seizures and observed a significant but moderate seizure reduction with subthalamic nucleus DBS. Dr. Devergnas then focused her lab's work on the thalamo-cortical loop and observed strong entrainment of the thalamic cells suggesting that modulation of this specific network might be helpful in desynchronizing cortical activity. Additionally, this model may manifest comorbidities similar to human patients. They recently validated the use of this NHP penicillin model to study the comorbid sleep disorder associated with seizures. Among the different nuclei implicated in sleep activity, they will now investigate the impact of seizures on the pedunculopontine nucleus and the lateral hypothalamus. Activity in both of these regions has shown to be related to control arousal and to regulation of rapid eye movement. Despite not being a classical epilepsy model, the NHP model of penicillin-induced seizures can help us to better understand the pathological mechanisms of seizures and to facilitate the development of new DBS therapies and technologies.

Cerebellar deep brain stimulation

The cerebellum is well-known for its important roles in motor behaviors including coordination, learning, and posture. However, recent work has revealed its involvement in cognitive behaviors such as language, emotion and reward. Consistent with its diverse

behavioral influence, cerebellar function is disrupted in ataxia, tremor and dystonia, as well as in autism spectrum disorders, schizophrenia, and obsessive-compulsive disorder. In a series of recent studies, Dr. Sillitoe and colleagues focused their attention on cerebellar motor function in order to test how a single brain region could contribute to such a wide variety of disorders (van der Heijden et al., 2021; Brown et al., 2022; Liang et al., 2022; Liu et al., 2022). They tested two hypotheses. First, they tested whether specific cerebellar connections may have a more predominant deficit in one disease versus another. Second, they tested whether distinct, abnormal neural signals could be produced in different cerebellar diseases. Using genetic manipulations and *in vivo* electrophysiology, the Sillitoe lab found evidence to support both hypotheses. They found that synaptic contacts onto Purkinje cells are differently, but not exclusively involved in ataxia, tremor and dystonia, and depending on the disease, distinct patterns of Purkinje cell to cerebellar nuclei miscommunication are initiated (van der Heijden et al., 2021). These results motivated them to test whether DBS could be targeted into the cerebellum as a means to compensate for or correct circuit defects and to potentially restore motion. They found that DBS directed to the interposed cerebellar nuclei, which are critical for ongoing motor functions, corrects movement in a range of motor conditions. These data raise the intriguing possibility of extending cerebellar DBS for use in neuropsychiatric conditions.

Advances and challenges in applying closed loop physiology to neuromodulation

The notion that a device-based approach could be used to decode symptoms and neurophysiology underpinning specific bothersome symptoms has provided excitement which has been driving the development of "closed-loop" or adaptive DBS. In practice, however, there have been formidable challenges as well as opportunities which will all need to be addressed in order to advance a practical and deployable approach.

At-home adaptive deep brain stimulation for Parkinson's disease using individualized neural biomarkers

Patients with PD can experience residual motor fluctuations during optimized continuous deep brain stimulation (cDBS). Previous in-clinic and short at-home studies have suggested that adaptive DBS (aDBS), i.e., titrating stimulation amplitude in response to symptom-state-associated neural signals (i.e., biomarkers), could possibly alleviate residual symptoms (Little et al., 2013; Arlotti et al., 2018; Gilron et al., 2021a). It has been uncertain if these results can be replicated at-home for sustained periods. Here, Dr. Cernera and Dr. Oehrn present a pipeline for developing at-home aDBS based on long-term intracranial recordings derived from the subthalamic nucleus (STN) and sensorimotor cortex of five PD patients implanted with the Medtronic Summit^{TM} RC + S system. Biomarker identification during stimulation was challenging, as stimulation can suppress or enhance frequency-specific neural activity and motor fluctuations during cDBS and these were not associated with STN beta oscillations (13–30 Hz) in all patients (Little et al., 2013). Therefore, it was necessary to explore the whole power spectrum beyond the beta frequency band and, if available, in multiple brain sites. Thereafter, aDBS parameters were selected in a data-driven manner and optimized parameters based on clinical effects during short-term testing (24 h). Using this pipeline, the first long-term at-home randomized double-blind comparison between aDBS and cDBS in one patient (4 weeks per condition in week-long blocks) using an individualized off-state biomarker (~12 Hz STN) revealed that aDBS increased on-time. Single-blind randomized comparisons between aDBS (8 days) and cDBS (5 days) in another patient using 65 Hz precentral cortical power as an on-state biomarker demonstrated that aDBS reduced dyskinesia and bradykinesia. These lessons could be possibly extended to other indications and could provide key insights for the development of at-home aDBS algorithms.

Closed-loop deep brain stimulation for Tourette syndrome

Tourette syndrome (TS) is a continuous lifelong syndrome that can be debilitating and stigmatizing for patients with moderate to severe motor and vocal tics that are resistant to medication and to behavioral intervention (Jankovic, 2001; McNaught and Mink, 2011). DBS has emerged as a promising treatment option for addressing medication resistant tics (Ackermans et al., 2011). Over the last few years, Dr. Gunduz and colleagues have demonstrated several key findings that provide the necessary foundation for a prospective trial to test closed-loop neuromodulation for tic suppression. They demonstrated that TS DBS could be successful even if not administered chronically and continuously (Okun et al., 2013; Rossi et al., 2016) which paved the way for closed-loop DBS. A follow-up study examined the thalamic activity in relation to tics recorded from contacts on the DBS lead (Molina et al., 2018). This study uncovered an electrical signal correlating both with occurrence of tic and with clinical improvement. Most recently, they reported thalamo-cortical network characteristics underlying tic generation through the use of deep DBS leads, along with chronically implanted subdural strips (Cagle et al., 2020). The technique was able to separate voluntary movement from tics and demonstrated that DBS could drive brain activity to a healthy, tic free state in the thalamus. These features allowed us to develop embedded closed-loop DBS for TS and to show its feasibility, safety and possible effectiveness when compared to conventional TS DBS for the treatment of tics (Cagle et al., 2022).

aDBS for intractable OCD: Progress and challenges

Ventral striatum (VS) DBS holds a FDA Humanitarian Device Exemption (HDE) approval for treatment of severe and intractable OCD. Although VS DBS reveals benefit in about 50–66% of cases, there is room for improvement in both clinical benefits and in reduction of DBS-induced behavioral side effects, especially hypomania (Goodman et al., 2021). Dr. Goodman and colleagues reported the preliminary findings from an NIH-funded study to develop adaptive DBS (aDBS) using devices that can both stimulate

and record (McLaughlin et al., 2021; Provenza et al., 2021). The study was conducted with the objective of identifying the neural based classifiers for OCD-related distress and DBS-induced hypomania. Building LFP based classifiers for psychiatric states can be challenging because most of our measures are subjective and not on same time scale as the neural recordings. Using computer vision machine learning approaches has been useful as a label for changing mood states. A combination of symptom provocations (e.g., tasks, exposure/response prevention therapy, and naturally occurring exacerbations) can be used to capture changes in OCD symptom severity. In the clinic setting, they use DBS induced mirth response and talkativeness as a proxy for hypomania. The Goodman lab is currently processing and analyzing LFP data time-locked with DBS, tasks, and activity during different behavioral states in the clinic setting and at home, in order to identify neural based classifiers associated with these states.

Transforming the OR into the laboratory

One shortcoming of neuromodulation research has been the ability of animal models to recapitulate the nuances of the human condition. Several laboratories have adapted the intra-operative environment to become a true laboratory. This approach is useful in understanding movement, speech, appetite or other human behaviors.

Understanding movement control during DBS surgery

Awake DBS surgery provides a unique opportunity to learn about movement control. Human bipedal walking involves the complex coordination of leg and arm swing between two sides of the body. How the primary motor cortex coordinates these precisely timed upper and lower extremity movements during locomotion is unknown. Dr. Wang's intraoperative team recorded subdural electrocorticography activities from the hand/arm area in the primary motor cortex of subjects undergoing DBS surgery who performed stepping and arm swing tasks (**Figure 2**). They showed that there were stepping-related low frequency oscillations over the arm area (Louie et al., 2022). Furthermore, they found that this oscillatory activity was separable, both in frequency and spatial domains, from gamma band activity changes occurring during arm swing (Louie et al., 2022). This low frequency activity during stepping could serve to entrain and to synchronize upper limb movements during walking. These findings broaden our understanding of motor cortical activity during gait and suggest a potential mechanism for coordinating multiple limb movements during bipedal walking.

Studying speech production during DBS implantation

Speech relies on basal ganglia-thalamocortical network activity, however ideas about how the basal ganglia modulates speech are primarily theoretical. The recent development of experimental paradigms to simultaneously record electrocorticography (ECoG) and subcortical activity during speech in patients undergoing DBS surgery, however, is providing insights into motor speech information coding within these circuits (**Figure 3**). It is important to note that research related ECoG collected during DBS surgery confers no defined risk to safety or accuracy (Panov et al., 2017; Sisterson et al., 2021). Initial speech studies focused on the STN, where microelectrode recordings revealed the presence of separate populations of neurons whose firing rates selectively decreased during speech planning or increase during speech production (Lipski et al., 2018). Consistent with a role in movement gain, STN gamma activity tracked with specific articulatory motor features, while the strength of theta/alpha oscillatory activity was associated with vocal gain adjustment (Chrabaszcz et al., 2019; Dastolfo-Hromack et al., 2022). In addition, the effort

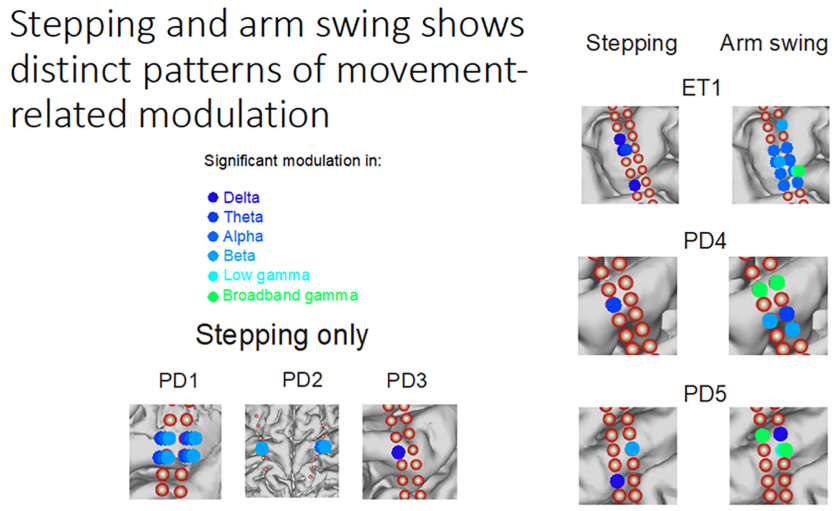

FIGURE 2
Stepping and arm swing shows distinct patterns of movement-related modulation–Subdural electrocorticography recordings demonstrate significant modulation of various frequency bands while performing different movement tasks. The modulation is unique from both a neuroanatomical perspective and an electrophysiologic perspective.

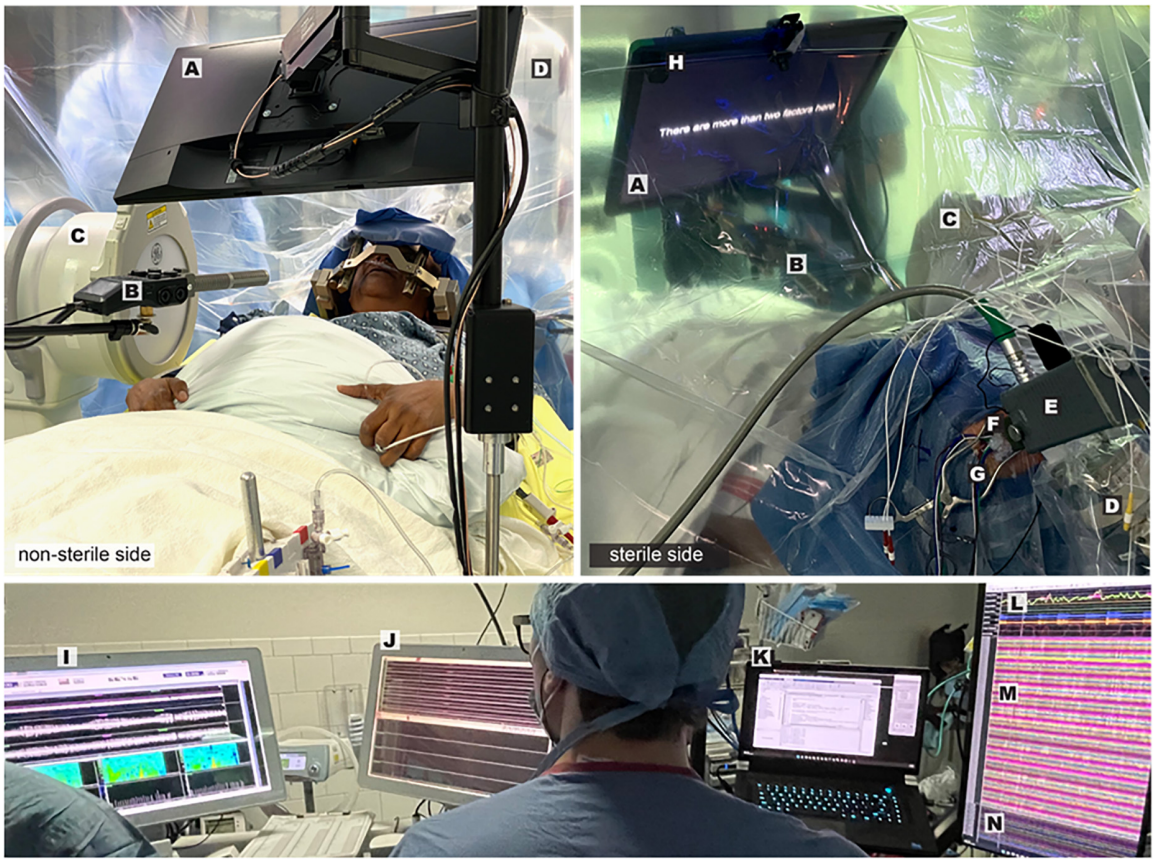

FIGURE 3
Intraoperative speech production research employing simultaneous cortical and subcortical recording–Views from the non-sterile (left panel) and sterile (right panel) sides of the operative drape show important components of the experimental and clinical set-up: Presentation monitor displaying a sentence stimulus **(A)**, boom microphone and recorder **(B)**, fluoroscopy machine **(C)**, robotic stereotactic arm **(D)**, microdrive **(E)**, tissue glue-filled 14 mm burr hole **(F)**, exiting wires from ECoG electrode strips **(G)**, photodiode **(H)**. Visualization of multiple synchronized recording streams is seen in the lower panel: clinical microelectrode signals **(I)**, macroelectrode signals and task triggers **(J)**, task control/data storage computer **(K)**, audio and respiratory signals **(L)**, ECoG signals **(M)**, DBS lead channels **(N)**.

required to produce novel words was reflected in increased gamma activity in both the STN and thalamus (Chrabaszcz et al., 2021; Wang et al., 2022). Methods previously established for antidromic mapping of the human hyperdirect pathway, using cortical potentials elicited from STN stimulation, provided evidence for monosynaptic connections from opercular speech cortex to the STN, including auditory cortex (Miocinovic et al., 2018; Chen W. et al., 2020; Jorge et al., 2022). These findings establish a basis for continued investigation of subcortical participation in speech planning and modulation, including the integration of information from sensory cortical areas participating in both feed-forward and feedback processes. Important additional factors for the future of this field will be the detection of speech artifacts in gamma frequencies and the need to engage patients proactively in intracranial human neuroscience experiments (Montreuil et al., 2019; Bush et al., 2022).

Provoking human nucleus accumbens representations of appetition

Dysregulation of mesolimbic circuits has been implicated in psychiatric disorders as well as in obesity. Increased power in low frequency oscillations have been reported to predominate in the mouse nucleus accumbens (NAc) during moments of heightened appetition (Wu et al., 2018). These field potentials were recorded specifically from the NAc shell subregion and exhibited significant spike-field coherence and correlated with an increased spike rate. Moreover, when used as a biomarker for responsive DBS, this low frequency domain effectively triggered brief bouts of DBS and reduced binge-eating behavior in mice. In an attempt to isolate these appetitive units within this NAc subregion in an ongoing first-in-human trial of responsive DBS for obesity (NCT03868670), tractographic segmentation of the human NAc was used and revealed a ventral posteromedial cluster, demarcating the homologous shell subregion (Cartmell et al., 2019). This territory and its prefrontal interconnections exhibited perturbed structural and functional connectivity in binge-prone obese patients, further implicating disease-specific dysregulation to be mapped during DBS (Barbosa et al., 2022). The Halpern lab used a protocol developed to provoke appetition as illustrated in **Figure 4** (Miller et al., 2019). Thus, physiologic representations of appetition within the human NAc defined by tractography may further inform spatial topography of this key mesolimbic node and may confirm patient-specific circuit engagement.

Cutting edge technologies from the industry sector

A key aspect to the success of the DBS Think Tank is the understanding that it will take industry and academic collaboration in order to advance neuromodulatory therapies into clinical practice. Each year we have an industry blitz to explore cutting edge therapies, challenges and opportunities in transforming science into product.

Innovation in DBS is dependent on cooperation between researchers and industry partners. In order to keep pace with discoveries in the research lab, industry must continue on a trajectory of progress that includes software and hardware innovation, and a trajectory that can incorporate new outcome measures, neurophysiological and biometric information, and the lessons gleaned from "big data." Highlights from industry revealed the development of new platforms to manage the increasing volume of data generated from patient-implanted devices and how the appropriate use of these data can lead to optimization of DBS with better power consumption and improved patient outcomes. Key concerns in this era of innovation include research platform access as well as data privacy and security. An open channel of discussion between researchers and industry engineers should be maintained, so that clinical research platforms and specialized settings can be accessed outside of commercial applications in order to facilitate experimentation. As data sets become larger and closed loop stimulation exits the laboratory setting and is accessible for the patient at home, security and privacy of data remain essential. Several manufacturers have already encountered novel questions about access to data, and these logistical and ethical issues must be part of the larger conversation on the future of data use.

Utilizing BrainSense technology to guide DBS therapy

In 2020, the Medtronic Percept^{TM} PC DBS device with BrainSense^{TM} technology received US FDA approval and EU CE Mark (Paff et al., 2020; Goyal et al., 2021; Jimenez-Shahed, 2021). The device is capable of delivering electrical stimulation therapy while recording local field potentials (LFP) through the same DBS lead. Since approval, more than 18,000 Percept^{TM} PCs have been implanted, uniquely enabling the chronic monitoring of brain activity in DBS patients during routine clinical care. The Percept^{TM} PC hardware platform is also upgradeable through software and firmware unlocks for performance enhancing and clinically meaningful updates.

The commercial availability of chronic LFP sensing also offers the potential to accelerate the pace of translational DBS research. Whereas Medtronic's first and second-generation DBS + sensing systems, Activa^{TM} PC + S and Summit^{TM} RC + S, have been utilized in dozens of investigational neurology studies, access to the technology was limited. In contrast, Percept^{TM} PC is now approved in the worldwide market for treating on-label indications including Parkinson's disease (PD), essential tremor (ET), dystonia, obsessive compulsive disorder (OCD), and epilepsy.

Unsurprisingly, brain sensing research has accelerated following Percept^{TM} PC approval. Initial studies in PD demonstrated that the LFP beta power strength (e.g., 13–30 Hz) correlates with patient akinetic rigidity symptoms and the responses to DBS and medication therapies (Feldmann et al., 2021, 2022; Koeglsperger et al., 2021); key replications of prior studies using investigational recording configurations (Neumann et al., 2016; Ozturk et al., 2020). Moreover, studies across multiple centers demonstrate the capability of Percept^{TM} PC to routinely detect LFP signals of interest in PD, ET, dystonia, OCD and epilepsy subjects with standard of care procedures (Fasano et al., 2021; Goyal et al., 2021; Thenaisie et al., 2021; Buijink et al., 2022; Vissani et al., 2022), which is also consistent with prior studies using investigational recording devices (Case et al., 2020; Darcy et al., 2022). Further, there is a growing body of case studies demonstrating the application of brain sensing for personalized treatment including initial DBS programming (Fasano et al., 2021; Sirica et al., 2021), DBS and medication optimization (Kern et al., 2022), and even understanding circadian patterns (van Rheede et al., 2022).

In parallel, there are nearly a dozen ongoing trials evaluating the safety and effectiveness of LFP-beta controlled adaptive DBS (aDBS) in PD using the Summit^{TM} RC + S or the Percept^{TM} PC aDBS unlock. In the US, EU and Canada the ADAPT PD approval trial (NCT04547712) evaluating aDBS has completed enrollment. In Japan, where aDBS is approved, early case study results are promising (Nakajima et al., 2021; Kimura et al., 2022; van Rheede et al., 2022) and continue to build upon the evidence for patient benefit suggested by previous investigational pilots (Little et al., 2013; Arlotti et al., 2018; Velisar et al., 2019). Finally, several physician-sponsored NIH BRAIN Initiative trials are applying the Summit^{TM} RC + S to investigate new indications including treatment resistant depression, Tourette's syndrome and opioid use disorder. Although the early experience with aDBS has been promising, experts at the DBS Think Tank discussed the battery drain issues associated with chronic sensing and the need to address these issues with rechargeables and potentially other technologies. Overall, this broad access to commercial DBS devices with embedded sensing technology has significantly impacted the journey toward personalized care strategies in established indications and biomarker discovery in new indications.

Toward personalized deep brain stimulation

Boston Scientific Neuromodulation (BSN) focuses on using data, algorithms, and stimulation technologies to personalize therapy for every patient through the following modalities:

Making imaging available during live programming, effectively aggregating prior neuroimaging and clinical data to aid in titration and leveraging analytics for faster DBS workflows. Platform supporting this vision, developed in collaboration with Brainlab Inc., include commercially available GUIDE XT and STIMVIEW XT which integrate BSN's Stimulation Field Models (SFMs) with automatic detection of lead location and orientation, and places these models in an auto-segmented, patient specific anatomy (Lange et al., 2021; Waldthaler et al., 2021). More recent advances include the DBS Illumina 3D algorithm which is an optimization algorithm that synthesizes imaging-based information to optimize SFM size, shape, and location to accelerate Image Guided Programming (Malekmohammadi et al., 2022). BSN is working to make this algorithm commercially available in the future.

Incorporating objective clinical measurements provided by external sensors into DBS programming using the DBS CLOVER search

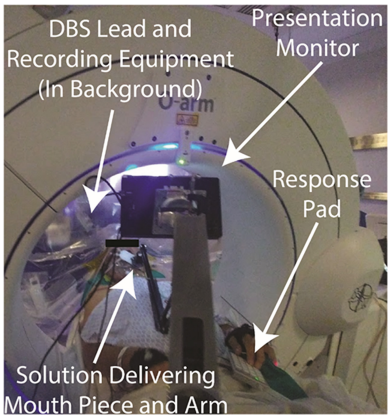

FIGURE 4
Intraoperative appetition provocation set-up.

routine. CLOVER suggests a stimulation setting, and after testing and assessing the clinical response, including using objective-measure wearables, the algorithm suggests next settings. The search continues until the improvement target for the assessed clinical response has been reached or the search space has been fully explored.

The first version of CLOVER delivered significant reduction of clinical symptoms in few steps using a single symptom; however, patients have clinical profiles including multiple symptoms (Sasaki et al., 2021; Wenzel et al., 2021). The new study with CLOVER uses a multi-symptom, weighted Patient Specific Metric as the input which synthetizes the global clinical state of the patient. The algorithm significantly reduces the UPDRS PIII scores (comparable to standard of care), and in fewer programming steps. BSN is working to make this algorithm commercially available in the future.

Enabling research on novel stim patterns to effectively explore the time domain aspects of DBS. Over the past decade, there has been increased interest in exploring temporal and spatial variations of DBS. To enable and accelerate research in this field BSN has released a new research software called Chronos (Wong et al., 2022). Chronos utilizes stimulation capability existant in Boston Scientific's rechargeable Genus stimulators to enable stimulation over an expanded range of frequencies and pulse-widths, bursting and cycling of stimulation on and off over multiple timescales, and generation of spatio-temporally complex patterns pulse-by-pulse. All stimulation delivered using Chronos enforces commercial charge density and amplitude safety limits and can be controlled using the patient's existing Remote Control. Chronos is intended for investigational use in selected studies, contingent on required approvals from Investigational Review Boards and, if required, IDE approval from the FDA.

Updates in neuromodulation for epilepsy

NeuroPace presently has three active clinical trials studying neuromodulation in epilepsy. The RESPONSE Study (ClinicalTrials.gov: NCT04839601) is a pivotal study to determine whether the RNS System is safe and effective as an adjunctive therapy in individuals ages 12 through 17 years who have drug-resistant focal epilepsy.

The NAUTILUS Study (ClinicalTrials.gov: NCT05147571) is a pivotal study to determine if the RNS System is safe and effective in individuals 12 years and older who have drug-resistant idiopathic generalized epilepsy (IGE). The study is a prospective, multicenter, single-blind, randomized, sham stimulation controlled pivotal study that will enroll 100 participants within the United States. Patients must have a confirmed diagnosis of IGE consistent with the ILAE Revised Classification of Seizures experiencing generalized tonic-clonic seizures (GTC), with or without myoclonic or absence seizures (Fisher et al., 2017). Leads will be placed bilaterally in the centromedian nuclei. Primary outcome measures are the 12-week post-operative serious device-related adverse event rate, and the time to second GTC seizure.

The RNS System Lennox-Gastaut Syndrome (LGS) Feasibility Study (ClinicalTrials.gov: NCT05339126) is an NINDS funded Brain Initiative study. The study is intended to generate preliminary safety and effectiveness data for brain-responsive neurostimulation of thalamocortical networks as an adjunctive therapy to reduce generalized seizures in individuals 12 years of age or older with LGS who are refractory to antiseizure medications. Up to 20 subjects will be enrolled. Pre-operative imaging will be used to create patient-specific maps of seizure networks, providing insight into how to personalize the treatment for each participant. Leads will be placed bilaterally in pre-frontal cortex and centromedian nuclei.

AlphaDBS is a new implantable closed-loop clinical neural interface

The AlphaDBS system features advanced filtering technology for detecting local field potentials (LFPs) sensed through the DBS lead (Arlotti et al., 2021; Marceglia et al., 2022). The implanted stimulator also utilizes a linear control algorithm that adjusts stimulation parameters according to the power in a selectable frequency band of LFPs. The system has 16 independently controlled stimulation and two sensing channels, one per hemisphere. *Via* a telemetry unit and a patient app, LFP data recorded 24/7 can be uploaded to a cloud-based database, with no data loss or overwriting. The fully implantable system has received CE-Mark for conventional DBS for the treatment of PD but not for adaptive DBS. The system is not FDA approved.

An external version of the system was tested in several recently published clinical trials in advanced PD patients with encouraging results suggesting that adaptive DBS improves clinical outcomes, specifically reducing dyskinesias. The fully implanted system has been tested in an ongoing pilot study in PD patients requiring an implantable pulse generator exchange utilizing the quadripolar leads already implanted in the STN. Six patients have been implanted to date. The system is characterized by reliable artifact-free recording and distributed neural data and signal management protocols (**Figure 5**). Alpha DBS's present application in the ongoing study represents a "proof of functioning" of a clinically viable implanted brain-computer interface (BCI) for adaptive DBS.

Real-world monitoring data can inform Parkinson's management

Basal ganglia LFP sensing, which is currently embedded in commercially available DBS devices, provides a rich dataset that may aid the development of personalized PD care. However, significant variability in electrophysiology, both within and between patients, must be taken into account when developing personalized treatments. There are many sources of variability, including, but not limited to the heterogeneous nature of PD, the expansive DBS stimulation parameter space and the effect of various medications. Modeling this variability will requires large and well-labeled data sets that link brain physiology to continuous objective metrics. These multimodal datasets can possibly be incorporated into routine clinical care to inform decisions about DBS – from patient selection, to DBS programming, to adaptive DBS (Gilron et al., 2021a,b; Fleming et al., 2022). However, collection and integration of these data require the development of new tools (Chen et al., 2021a). Using Rune Labs, we show an example of one patient who was continuously monitored for an entire year before and after implantation using a sensing enabled DBS, and we highlight ways in which this dataset paints a rich picture as compared to standard clinical scales. Notably, you can observe the variability in tremor fluctuations throughout the year with standard clinical tremor scores only capturing a small subset of this variability (**Figure 6A**). Both tremor and average STN beta were reduced as tremor was increased during routine clinical care (**Figures 6B, C**). Taken together, this highlights the role in which rich datasets pairing chronically recorded neurophysiology and objective data may be used to develop models that can inform stimulation or medication titration.

The DBS Think tank has encouraged global participation and in that spirit advances from Asia, Europe, and Australia were all covered.

Updates from Europe

Advancements in deep brain stimulation for psychiatric disorders

Deep brain stimulation (DBS) was introduced for the treatment of psychiatric disorders at the end of the 20th century, beginning with Gilles de la Tourette syndrome (GTS) and OCD. Since that time, the potential of this treatment has been further explored for other psychiatric indications in otherwise treatment resistant patients. A current meta-analysis conducted by Wehmeyer et al. (2021) summarized the results of studies with DBS in GTS and demonstrated that chronic DBS with different targets was associated with significant tic-reduction, with pallidal stimulation in this paper showing a possible advantage. Connectivity studies facilitated a more individualized approach for GTS patients with different symptoms and different comorbidities.

The effectiveness of DBS for OCD has been shown in several recent studies with different brain targets such as the medial dorsal nucleus of the thalamus, ventral anterior nucleus of the thalamus, medial forebrain bundle, subthalamic nucleus and inferior thalamic peduncle (Mallet et al., 2008; Maarouf et al., 2016; Lee et al., 2019). In a recent study from Li et al. (2020), a unified pathway between the dorsal anterior cingulate, ventrolateral prefrontal cortex and the anteriomedial STN was identified and was associated with a beneficial clinical outcome. These results could be replicated in further follow-up studies in different sets of patients. Several targets have also been described for treatment resistant depression. A recent study from Coenen et al. (2019) showed a long-term antidepressant effect of superolateral medial forebrain bundle DBS in a sham-controlled trial.

Deep brain stimulation (DBS) for patients with pathological aggressiveness and self-injurious behavior continues to be a controversial therapy option. A case-series from Torres et al. (2020) demonstrated a favorable long-term clinical outcome in the majority of patients with hypothalamic DBS. In summary DBS has proven to be an effective treatment option in several psychiatric disorders and there may be other indications emerging.

Adaptive DBS for movement disorders—opportunities with externalized DBS hardware

The recent advent of sensing-enabled DBS has facilitated the recording of neural signals from chronically implanted electrodes during unconstrained activity and activity occurring in a naturalistic environment. Comparatively, perioperative subcortical sensing when the DBS electrodes are temporally externalized has been performed for more than 20 years. Despite the limitations of the methods on short recording time, constrained testing environment and potential stun effects, working with externalized patients offers unique advantages for research including: excellent signal to noise ratio, high sampling rate, and the possibility of accurately synchronized recording of other signals such as EEG, MEG, and EMG. These methods could offer new insights on the underlying circuit pathophysiology, and how cortical and subcortical neural oscillations could translate into muscle activities in behavior. It also could offer unique opportunities to test new algorithms and hardware, without being limited by what is feasible with an existing implantable device.

There are a few projects which demonstrate how we are taking advantage of this research opportunity to: (1) better understand the role of STN in gait control and to drive forward adaptive DBS for gait difficulties; (2) to explore the use of a machine learning based approach to detect specific brain states to drive closed-loop DBS for essential tremor; (3) to test and to compare different signal processing and control algorithms for adaptive DBS for PD while using beta amplitude as the feedback signal; and (4) to design and to test a new translational neuroscience research tool with improved performance on sensing during the actual stimulation.

Deep brain stimulation for non-motor symptoms in Parkinson's disease

Parkinson's disease is associated with a multitude of non-motor symptoms (NMS) throughout the course of disease (Chaudhuri and Schapira, 2009). Sleep, autonomous functions, urogenital control, sensory perception and in particular mood and cognitive function can be impaired and have a profound impact on quality of life. Although often overshadowed by the visible motor fluctuations, NMS motor symptom severity also fluctuates with brain dopamine levels and can improve with continuous dopaminergic stimulation. This

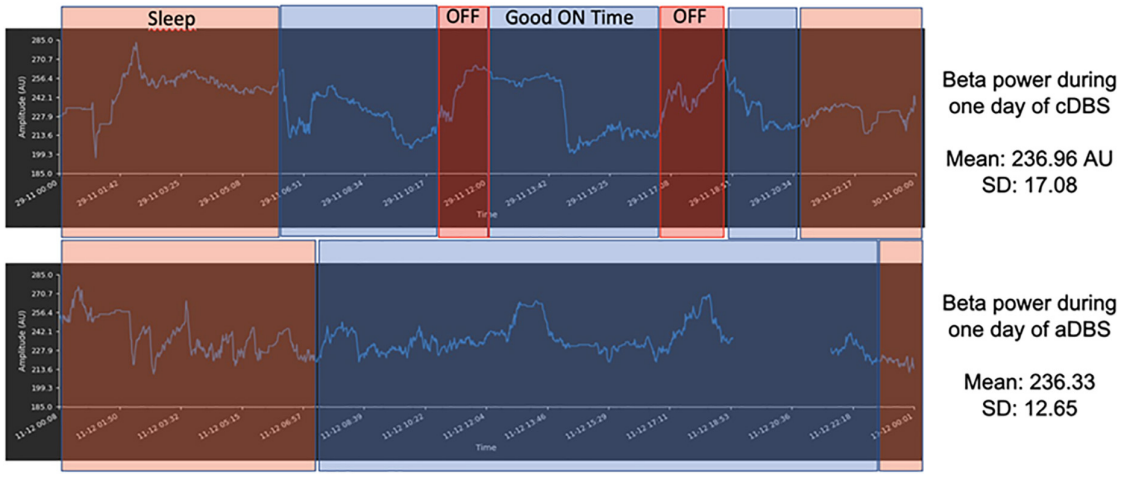

FIGURE 5
Example of 1 day recording with matched diary features–Sleep–orange rectangles; OFF time–red rectangles; ON time without troublesome dyskinesias (Good on Time)–blue rectangles for AlphaDBS system in cDBS **(top row)** and aDBS **(bottom row)**. The x-axis is time (sampling frequency: 1 min) and the y-axis is beta power amplitude (arbitrary units–AU). The signal displayed was stored within the AlphaDBS IPG with the patient at home and was uploaded to the cloud system *via* telemetry and patient app, according to the data management protocol.

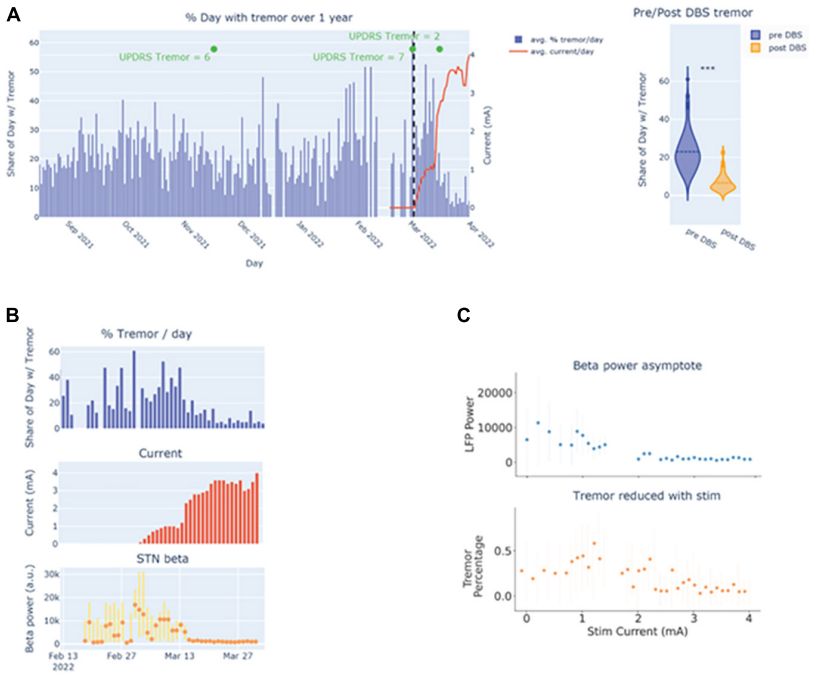

FIGURE 6
(A) Visualization of tremor burden over time. **(B)** Viewing the temporal relationship between tremor burden with stimulation amplitude and beta power. **(C)** Visualizing the relationship between tremor and beta power with stimulation amplitude.

indicates that at least some NMS may result from hypodopaminergic brain circuit dysfunctions, while others are thought to reflect neurodegenerative loss of function. Deep brain stimulation has been used to explore the pathophysiology of several NMS in a systematic approach by comparing the effect of a levodopa challenge to a targeted intervention in the basal ganglia loop on non-motor readouts (Dafsari et al., 2018; Petry-Schmelzer et al., 2019; Reich et al., 2022). STN-DBS was shown to have direct impact on a central brain circuit regulating urinary bladder sensation and thereby reducing urinary urgency in PD (Herzog et al., 2006). Likewise emotional perception, drive and mood were elevated by STN-DBS in acute stimulation experiments to a similar extent as during an acute levodopa challenge. Neuroimaging and connectomic studies indicate that the optimal stimulation site for NMS within the subthalamic nucleus may differ slightly from the motor sweetspot of STN-DBS, but better tools for objectively and reliably measuring NMS may be required for mapping the NMS effects of DBS (Petry-Schmelzer et al., 2019).

Impulse control disorders, hypomania, compulsive levodopa intake and hyperactivity in advanced PD have been ascribed

to dopaminergic sensitization following a similar mechanism as dyskinesia induction by pulsatile dopamine replacement therapy. These hyperdopaminergic NMS may also indirectly benefit from subthalamic DBS due to reduced medication requirements (Lhommée et al., 2012). First clinical evidence has demonstrated a favorable impact of STN-DBS on hyperdopaminergic behavioral symptoms in PD, which evolves over several months in parallel with dopaminergic drug withdrawal. In summary, non-motor does not mean non-treatable and NMS burden should therefore be evaluated and stratified for a potential therapeutic impact during the selection process for DBS surgery.

Updates from Asia

Insights from modulation of intracranial recordings on cognitive processes

Recent studies by Dr. Voon and colleagues focus on stimulation-sensitive biomarkers by investigating local field potential physiology in the context of cognitive processes and its sensitivity to time-locked stimulation. In her discussion, Dr. Voon highlights studies focusing on the STN in PD. First, she showed that the physiology underlying objective markers of risk can be dissociated from subjective betting (Manssuer et al., 2022). High frequency acute STN stimulation decreased the risk taking possibly through modulating STN theta frequency. STN DBS was associated with increased impulsivity with hastened "responding under conflict." These findings emphasize the heterogeneity of impulsivity with potential implications for disorders of addiction. Second, she showed the capacity to enhance subjective positive emotional bias through targeting the late alpha desynchronization to affective stimuli by using alpha-specific frequency acute STN stimulation which enhanced alpha power. Patients with depressive symptoms appeared to have a greater positive bias to alpha frequency rather than high frequency stimulation, again highlighting the potential impact on comorbid depression. Further updates from ongoing randomized controlled trial studies in China include: major depression targeting the bed nucleus of the stria terminalis demonstrating changes in low frequency oscillatory activity with improvements in depression; multicenter studies targeting nucleus accumbens and ventral internal capsule for opioid use disorder and obsessive compulsive disorder.

DBS in China, from clinical to clinical research

Closed-loop neuromodulation is an inevitable trend of the expansion of DBS and naturally, it is also a research hotspot. Closed-loop DBS does not use additional electrodes to collect brain data, but relies on the stimulation electrodes. Closed-loop DBS could synchronously record LFPs of the target brain area during stimulation, especially recording long-term outcomes (Qian et al., 2016). Therefore, closed-loop DBS will become more important and could shed light on the chronic DBS mechanism. To accurately describe the information from the deep brain target, it will be necessary to remove the artifacts, for which a lot of preliminary preparations have been made (Qian et al., 2017a,b; Chen et al., 2021b,c). Based on 6 months recordings of STN-LFP signal, Dr. Li and colleagues recently reported the potential characteristics of chronic neuromodulation effects in the stimulated target (Chen Y. et al., 2020). By making chronic synchronous recording possible, closed-loop DBS could be regarded as a fully-implantable brain-machine interface (BMI). Recently, the Li lab investigated the performance of using a closed-loop neurostimulator as a motor BMI (Chen J. C. et al., 2022). By decoding movement from STN-LFP information, the system achieved a typical two-dimensional center-out task to simulate virtual wheelchair control.

In 2020, Shen et al. (2020) reported the first systematic work of studying the DBS regulatory mechanism based on 3T magnetic resonance compatibility technology (Jiang et al., 2014; Bai et al., 2016; Zhang et al., 2019). The authors conducted follow-up studies after 1, 3, 6, and 12 months of implantation of bilateral STN in 14 PD patients. With a block-design that interleaved stimulation on and off while performing fMRI, the brain function states were analyzed with high repeatability and reliability. The authors observed that STN-DBS could regulate the cerebellum. Two distinct circuits showed different frequency and time-dependent modulatory effects. The circuit involving the globus pallidus internus (GPi), thalamus, and deep cerebellar nuclei was sensitive to stimulation frequency and was more activated under high-frequency. The circuit involving the primary motor cortex (M1), putamen, and cerebellum was deactivated and remained unchanged under different frequencies. In contrast, deactivation in the M1 circuit was gradually enhanced over time, however the GPi circuit revealed no change.

Role for the amygdala in treatment-refractory obsessive-compulsive disorder using deep brain stimulation

The neural basis for OCD, a disabling psychiatric condition with a lifetime prevalence of 2–3%, is uncertain (Gadot et al., 2022). The classical neurobiological models of OCD based primarily on dysfunctional parallel cortico-striatal loops have been questioned, while the precise role of other implicated brain regions, such as amygdala and cerebellum, also remains unclear (Kammen et al., 2022). Here the Queensland Brain Institute report single unit recordings from the BNST region during DBS implantation which showed that action potentials were broader in patients with more severe OCD. Functional neuroimaging data collected before electrode implantation showed enhanced amygdala and cerebellar responses to negative emotional pictures in OCD patients as compared to healthy controls. Cerebellar vermis responses to negative pictures explained 97.2% of inter-subject symptom variance in OCD patients. Functional connectivity between amygdala and cerebellar vermis predicted 95% of inter-subject variance in OCD symptoms following 23 weeks of DBS therapy applied to the bed nucleus of the stria terminalis within the extended amygdala. These results indicated a crucial role for amygdala-cerebellar functional connectivity in mediating OCD symptomatology and the therapeutic effect of DBS.

The DBS think tank deliberately and proactively addresses neuroethical issues and dilemmas facing the field. Emerging issues included measuring what matters, informed consent and in addressing legal issues in psychiatric neuromodulation.

Neuroethics cases: Dilemmas that inform the future of neuromodulation

Measuring what matters

Empirical data can be used to demonstrate that commonly used patient outcome measures do not assess patients' primary goals for pursuing DBS for PD. Similarly, existing personality measures do not fully capture the public understandings of personality. Our empirical data highlight that DBS used to treat the motor symptoms of PD significantly helps patients achieve their behavioral goals and may be restorative to the patients' most valued personality characteristics. Additionally, their ratings following DBS could possibly be "closer" to retrospective ratings reflecting their personality prior to disease onset.

These observations highlight the importance of soliciting a patients' perspective and their lived experiences in order to develop better outcome measures. Outcome measures that are more relevant to patients' perspectives, values, and goals are directly related to best informed consent practices. Our recommendations extend to neuromodulation trials for other indications, particularly neuropsychiatric trials in which the behavioral goals and personality factors may be complex and nuanced. We encourage other clinical research teams to systematically assess patients' goals and values and to incorporate outcome measures better reflecting those values. We highlight the need to include the voices of under-represented minorities who have been historically ignored in an effort to ensure that we do not inadvertently perpetuate healthcare inequities and assume that the data collected (primarily from white participants) reflect other groups values and goals. Partnerships with humanities scholars will be essential for expanding the promotion of more patient centered, inclusive healthcare within neuromodulation.

Ethical issues in intraoperative neuroscience research: Assessing recall of informed consent and motivations for participation

The use of neurosurgical patients as human research subjects raises important ethical considerations, yet a thorough empirical examination of these issues in a participant population has been lacking. The Wexler lab aimed to empirically investigate the ethical concerns regarding informed consent and voluntariness in PD patients undergoing DBS participating in an intraoperative neuroscience study. Two semi-structured 30-min interviews were conducted preoperatively and postoperatively *via* telephone. Interviews assessed a subjects' motivations for participation in the parent intraoperative study, recall of information presented during the informed consent process, and postoperative reflections on the research study. Twenty-two participants completed preoperative interviews and twenty participants completed postoperative interviews. All participants cited altruism or advancing medical science as "very important" or "important" in their decision to participate in the study. Only 22.7% (n = 5) correctly recalled one of the two risks of the study. Correct recall of other aspects of the informed consent was poor (36.4% for study purpose; 50.0% for study protocol; 36.4% for study benefits). All correctly understood that the study would not confer a direct therapeutic benefit to them. Though research coordinators were properly trained and the informed consent was administered according to protocol, participants demonstrated poor retention of study information. While intraoperative studies aimed to advance neuroscience knowledge may represent a unique opportunity to gain fundamental scientific knowledge, improved standards for the informed consent process can help to facilitate ethical implementation.

Psychiatric neurosurgery laws and incapable patients: What would a model law say?

Mental health legislation in multiple countries, specifically addressing neurosurgery for psychiatric disorders, includes psychiatric applications of DBS within the scope of the laws (Nadler and Chandler, 2019; Chandler et al., 2021). Many of these laws are quite recent (Mental Health Act, Scotland, 2003; Mental Health Act, Australia, 2014; Mental Healthcare Act, India, 2017), revealing continued social and legal attention to neurosurgical treatments especially to address psychiatric conditions. These laws often address the following general issues: restricted eligibility of particular populations for psychiatric neurosurgery (particularly incapable patients, children, prisoners and involuntarily hospitalized patients), independent pre-surgical approval processes sometimes including courts or mental health tribunals, and record-keeping and post-surgical reporting requirements (Chandler et al., 2021). The 1977 report on psychosurgery by a US National Commission made recommendations in each of these areas. The report also suggested that it would be unfair to categorically exclude certain groups of patients from access, despite concerns about the use of invasive neurosurgery (United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1977). If and when evidence builds about the efficacy of DBS for psychiatric purposes, this question may become more pressing for jurisdictions that currently exclude particular populations from access, in order

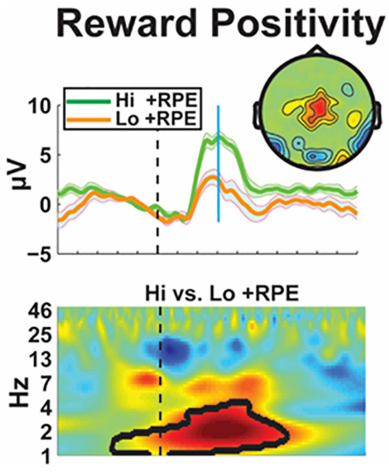

FIGURE 7
Electrophysiological characterization of reward positivity–An electrophysiological biomarker of the ventral reward system is demonstrated by the positive reward prediction error (+ RPE). This signal can be seen when receiving a "highly surprising reward" (Hi + RPE) or an "expected reward" (Lo + RPE) after a task. This differential effect can then be used to identify electrophysiologic associations with the reinforcement learning test paradigm to characterize reward value.

to protect them from harm. A critical part of the path forward will be ensuring that the views of people who have severe mental health challenges will be included as central in the discussion about the legal regulation of this field. A further legal question of importance will be how mental health care funding parity and anti-discrimination laws in countries with various health care funding models might influence the underfunding of all mental health care; perhaps including DBS for psychiatric applications.

DBS candidacy: The next frontier in emerging therapies

An important area in neuromodulatory therapies has been identification of candidate biomarkers, use of AI technology and building wire diagrams for translational neuroscience. The DBS Think Tank addressed the emerging issues in the DBS field.

Identification of candidate neural biomarkers of obsessive-compulsive symptom intensity in ecologically valid environments

Despite the success of DBS for the treatment of refractory OCD, there are currently no robust neural signatures for obsessive-compulsive (OC) symptoms. This shortcoming may be due to limited opportunities available for conducting intracranial electrophysiological recordings in natural environments where fluctuations in symptoms may occur. Recently available DBS platforms offer a way past this hurdle, allowing for streaming of intracranial neural activity both at home and in the clinic. Here, our goal was to identify neural correlates of OC symptom intensity. Provenza et al. conducted longitudinal intracranial recordings in five participants with refractory OCD implanted with recording-capable DBS devices targeted to the ventral capsule/ventral striatum (VC/VS) or bed nucleus stria terminalis (BNST). Provenza and colleagues captured LFPs at home during naturalistic exposures to OCD triggers. All five participants who completed the study were clinical responders to DBS therapy. Using the intracranial data collected during OCD exposures, the team computed correlations between spectral power and OCD symptom severity. They then identified low delta-band power as a candidate neural biomarker of OC symptom intensity during symptom provocations in one participant (left VC/VS: $R = -0.59$, $p = 0.01$; right VC/VS: $R = -0.56$, $p = 0.04$) (Provenza et al., 2021). This signal has potential utility for classification of symptom intensity in adaptive DBS systems for OCD. Continued opportunities for long-term, naturalistic intracranial electrophysiological recordings will help to propel biomarker discovery for OCD and other psychiatric disorders.

Building a wiring diagram of the brain: Tools for translational neuroscience

The efficacy of DBS is highly dependent on targeting the "right" connections. Mapping anatomical connectivity of the human brain is not a straightforward task, particularly when it comes to white matter organization. The Heilbronner lab has worked on the methodologies used to uncover anatomical connectivity. Diffusion tractography, for example, is applicable in humans and can be used to interrogate the connectivity of the whole brain, but it frequently fails to generate accurate fiber trajectories. Anatomical tract-tracing, by contrast, is highly accurate, but has been limited to use in non-human animal models and is fundamentally not whole-brain. Dr. Heilbronner highlighted how deliberately cross-species and cross-modal pipelines can help us to achieve more accurate wiring diagrams of the human brain as a method to aid in neuromodulation. These diagrams can provide neuroanatomical underpinnings of complex behaviors and resting-state fMRI results.

A novel, simple, rapid, and inexpensive biomarker of the ventral reward system

Electrophysiology (EEG) is a direct measure of neuronal processes, and it is uniquely sensitive to canonical neural operations that underlie emergent psychological operations. These qualities make EEG well-suited for the identification of aberrant neural mechanisms that underlie complicated disease states. The Cavanagh lab reviewed the qualities of a novel biomarker of the ventral reward system: the event-related potential component known as the Reward Positivity (RewP). The RewP emerges as an over the cortical midline as a positive polarity deflection from ~200–500 ms following reward receipt. The RewP is not only specifically elicited by rewards, but it is also sensitive to the major computational construct used to define reward value: RewP amplitude scales with the degree of the positive reward prediction error. They presented the magnetoencephalographic source estimation that the RewP is generated by ventromedial prefrontal cortex (**Figure 7**). Moreover, they showed that the diminished RewP in major depression is likely due to hypoactivity in these areas, including subgenual cingulate. Translational applications of the RewP will be presented, including a novel mouse model which will facilitate bench-to-bedside applications. The RewP will be contrasted with an established mechanistic biomarker of cognitive control: frontal theta band activity, which is reliably enhanced in anxiety disorders. Together, these findings will motivate the use of EEG biomarkers, including frontal theta and the RewP, for assessing the efficacy of psychiatric deep brain stimulation on canonical neural circuits.

What's next for clinical neuromodulation

An important aspect of neuromodulatory therapy is asking the question what's next? New approaches for dystonia DBS have been moving into clinical practice. The use of AI is getting closer to informing clinical decision making. We discussed the idea that there may be a return to "brain lesioning," and how the field is moving closer to true brain-computer interfaces.

Cerebellar neuromodulation for acquired dystonia

Dystonia in the setting of cerebral palsy (CP) is the most common cause of acquired dystonia in childhood, and its management can be

challenging. DBS of basal ganglia or thalamus has played a major role in the treatment of isolated dystonias, however its efficacy in dystonic CP is lower. This may be due to underlying structural damage, lack of improvement of comorbid choreoathetosis and spasticity, and an increased risk of hardware complications.

The cerebellum may represent an alternative brain target for dystonic CP. It has a recognized role in dystonia pathophysiology; it is frequently spared from hypoxic ischemic damage, and small studies have shown the promise of cerebellar stimulation in improving spasticity and CP-related movement disorders.

Dr. San Luciano presented preliminary data from three dystonic CP participants with bilateral cerebellar DBS targeting the dorsal (microgyric, motor) dentate nucleus using Medtronic Percept. Cerebellar LFPs were recorded and a prominent alpha rhythm (~10 Hz) was identified, which decreased in amplitude and variance at higher stimulation amplitudes, a possible physiomarker of dystonia. Beta band peaks (~20 Hz) were also present. All participants experienced subjective variable improvements in symptoms, including in hand coordination, head control, speech clarity and fluency and perceived limb tightness, collectively representing ~20–40% rating scale improvement.

Dr. San Luciano and colleagues proposed a larger study of cerebellar DBS in children and young adults with dystonic CP. They will characterize cerebellar LFPs related to clinical assessments, wearable monitors, and relation to stimulation; perform pre and post- postoperative volumetric structural and functional MRI and diffusion tensor imaging to identify candidate imaging markers of baseline disease severity and response to DBS, and to test its efficacy for improving quality of life, clinical assessments and objective kinematic metrics in an N-of-1 clinical trial design.

Informing clinical decisions in psychiatric neuromodulation with AI

When pursuing new DBS indications, we must establish clinical guidance in each step of the process, including patient selection, DBS targeting, and ongoing therapeutic decision making. This "decision making step" is especially challenging in depression, where common assessment methods are often based on surveys with known biases and that can reflect non-specific symptoms. As a specific example, depression DBS patients often experience instability in measures such as the Hamilton Depression Rating Scale (HDRS), and clinical teams must determine if the HDRS increases reflect worsening depression (indicating dose adjustment) or transient mood disturbances not warranting intervention. Dr. Rozell presented their ongoing work using longitudinal LFP recordings from subcollosal cingulate DBS patients and novel explainable AI techniques to develop objective biomarkers of stable recovery. In addition to showing generalization of the derived biomarkers across multiple patient cohorts (with different clinical teams and implantable devices), they showed a series of case studies illustrating how this biomarker could support clinical decision making during DBS therapy. These case studies included responding patients with HDRS increases due to transient anxiety, and scenarios where relapses (reflected in HDRS scores) were significantly preceded by biomarker changes that could have indicated the need for therapeutic intervention.

Is the future of DBS a return to brain lesions?

Historically, brain lesions provided the foundation for localization of symptoms and were used as a treatment for brain diseases. One of James Parkinson's original 6 patients experienced relief of tremor following a focal stroke. This serendipitous observation motivated neurosurgical interventions, eventually leading to DBS. While the past of DBS has been based on lesions, many assume that the future of DBS is based on electrophysiology. Significant effort is being put into identifying electophysiological biomarkers and targeting these biomarkers with adaptive or closed loop stimulation, and great progress has been made. However, an alternative (and controversial) possibility is that the future of DBS is actually a "return to brain lesions." Recent advances have improved our ability to map lesion-induced effects to specific brain circuits, including lesions that provide relief of symptoms such as tremor or addiction. These lesion-based localizations align with DBS benefits and side effects such as memory decline and depression. Improved localization can lead to more precise neuroanatomical treatment targets, which may mitigate the traditional advantages of DBS over lesions such as "reversibility and tunability." New tools for creating brain lesions such as high intensity focused ultrasound could facilitate lesions to be placed without a skin incision and are already in clinical use for tremor. Although there are limitations and caution is warranted with irreversible lesion-based interventions, improved precision may 1 day make lesions preferable over DBS. In summary, improvements in lesion-based localization are refining our therapeutic targets and improved technology have been providing new ways to create lesions, which together may lead to a change in the relative value of DBS versus lesions.

Emerging consumer BCI

Controlling computers with human brain signals is quickly becoming a reality through brain-computer interfaces (BCI). Development of BCI devices has been based on academic research that has largely contributed to our understanding of brain functions. Over the past decade many laboratories have dedicated their research to improving our knowledge on how neurons in the brain encode movements, decision, and behavior. Dr. Henderson's lab (among others) investigated movement-related signals in human motor cortex to advance neural prosthetics, including translation of a high-performance neural prosthesis (Gilja et al., 2015), typing at ~8 words per minute using a brain-controlled cursor (Pandarinath et al., 2017), control of a tablet computer using neural signals (Nuyujukian et al., 2018), and high-performance brain-to-text communication using decoded handwriting (Willett et al., 2021). These innovations have helped to demonstrate the potential practical uses for an interface between the brain and a computer system.

Today, many companies have integrated this BCI technology into their roadmap. Neuralink, led by CEO Elon Musk, is one of the most advanced BCI companies in the field and has been developing a fully-implantable, wireless, high-channel-count device and an automated robotic system for reliable and efficient implantation (Musk and Neuralink, 2019). This system, called the link, records neuronal activity, decodes the information through AI algorithms and sends a command back to the computer. It has been successfully implanted

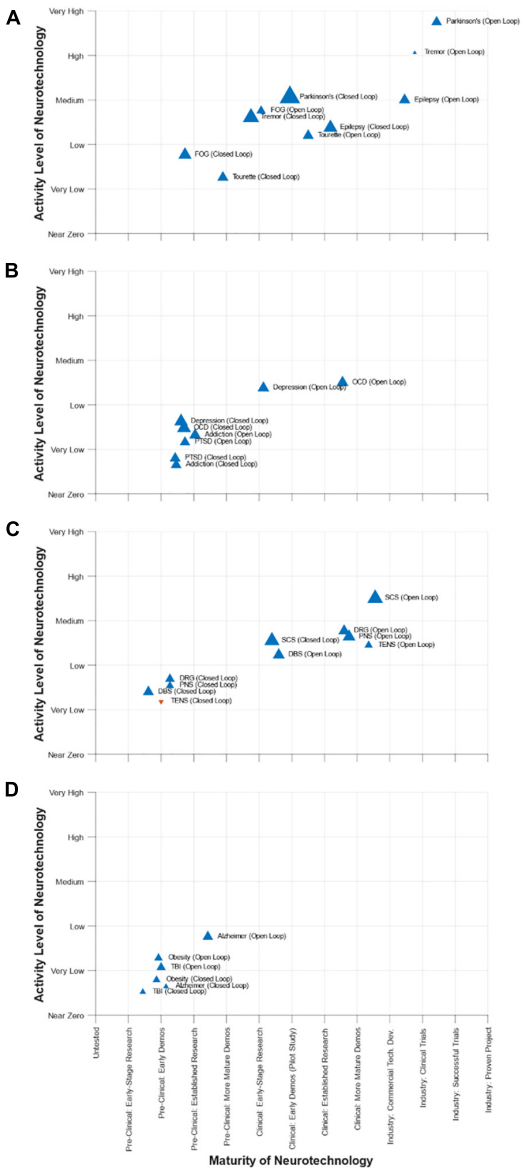

FIGURE 8
DBS-Think-Tank Neurotechnology Activity-Maturity Graphs–This figure presents four graphs that illustrate the perceptions of DBS-Think-Tank attendees about the maturity, activity, and change in activity of a variety of neurotechnologies. The neurotechnologies are organized into the following four groups and graphed separately: **(A)** movement disorders, **(B)** psychiatric disorders, **(C)** pain disorders, and **(D)** other syndromes. The upward pointing blue triangles represent increasing activity and downward pointing orange triangles represent decreasing activity. The magnitude of the rate of change is proportional to the size of the triangles. The definitions of the abbreviations used to identify each triangle are as follows: DBS, deep brain stimulation; FOG, freezing of gait; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; PNS, peripheral nerve stimulation; TENS, transcutaneous electrical nerve stimulation; DRG, dorsal root ganglia stimulation; SCS, spinal cord stimulation; TBI, traumatic brain injury. The data presented were derived from a survey that had a total 45 respondents. Characteristics of the respondents were as follows: affiliation (75% academic, 20% industry, 5% government), background (89% clinical research, 57% technology development, 52% engineering, 45% provider of clinical care, 23% biological science, 14% technology commercialization, 11% fund research and/or development, 11% physical science, 7% entrepreneurship, 5% regulation, 5% reimbursement, 5% management/administration, and 2% patient), and years of experience (18% with 0 to 5 years, 25% with 5 to 10 years, 23% with 10 to 15 years, 18% with 15 to 20 years, 11% with 20 to 25 years, and 5% with 25 to 30 years).

and tested in non-human primates and is nearing clinical trials to provide assistance for people with neurological disorders. Other companies using different technology to record and stimulate the brain are also emerging. Motif Neurotech is a new company that aims to stimulate the brain through magnetoelectrics, a process by which oscillating magnetic fields are converted to oscillating electric fields (Chen J. C. et al., 2022). This technology uses a miniature neurostimulator the size of a pea that can be delivered with minimally invasive surgical techniques and will stimulate neural tissue without the need for wires or batteries. An external power source, housed in a wearable, will provide the energy and stimulation pattern. To maximally leverage the advantages of this technology, the initial applications will focus on disorders not requiring continuous stimulation, as compliance with use of the wearable will be challenging. Disorders that can be successfully treated with episodic therapy such as transcranial magnetic stimulation (TMS) may be ideal targets. Individuals with psychiatric disorders, for example, often respond to TMS therapy, but relapse rates are high. The ultimate neurostimulation strategy will be designed to allow individuals to deliver therapy from home, using a convenient and effective dosing plan.

Clinically viable BCI will likely be soon available to help people with medical conditions. However, BCI is emerging as the next "trendy" technology and expending beyond the medical application. There is consensus that consumer BCI will soon be part of everyday life. Although we should not be scared of this BCI emergence, it is important to understand these technologies and to assess the risks associated. These risks and issues will inform effective policies to protect users. Data privacy and sharing, full disclosure on the system capability and limitations, responsibility of the company beyond clinical trials will all be important risks. These risks should be debated and proactively addressed with industry as an equal partner.

Conclusion

After the conference, the DBS Think Tank participants completed a survey that captured their views about the maturity, activity level, and rate of growth (or reduction) in activity for the use of neurotechnology to address selected movement disorders, psychiatric disorders, pain, and other conditions. The results from the survey are summarized in **Figure 8**. A key feature of the survey was the assessment of open-loop and closed-loop neuromodulation therapies for each condition. Although the maturity of closed-loop neuromodulation is nascent to non-existent for some indications, it is showing great promise for others. It will be interesting to see the creation, evolution, and growth of closed-loop neuromodulation in the years ahead and the ability of the DBS Think Tank community to anticipate it.

This year, the DBS Think Tank X sessions were all led and organized by women leaders in neuromodulation. The DBS Think Tank X traced the milestones in depression DBS and we discussed the re-introduction of a major clinical trial in this area. The Think Tank X addressed both the challenges and opportunities for adaptive or for closed loop DBS. There was discussion as to whether the closed loop approach would be optimal for "all patient groups" or will be more appropriate for select groups of individuals with specific symptom profiles. The DBS Think Tank X discussed the emergence of new targets, electrical biomarkers, AI and challenges in neuroethics especially as we move closer to true brain-computer interfaces. It was

clear from the 3 days of discussion that many groups are using animal models to drive the science along with true intra-operative research approaches. The neuromodulation field continues to rapidly grow with an estimated 244,000 implants worldwide.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the individual academic institutions. All participants provided their written informed consent prior to participation in the studies. The animal study was reviewed and approved by individual institutional animal welfare committees at the respective academic institutions.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

HM received consulting and IP licensing fees from Abbott Labs. WG received consulting fees from Biohaven and royalties from Nview, LLC and OCDscales, and LLC. EP had received research support from Mainstay, Medtronic, Neuros Medical, Nevro Corp, ReNeuron, SPR, and Saluda, personal fees from Abbott Neuromodulation, Biotronik, Medtronic Neuromodulation, Nalu, Neuros Medical, Nevro, Presidio Medical, Saluda, and Vertos, and holds stock options from SynerFuse and Neuro42. JV had received consulting fees and grant support by Medtronic and Boston Scientific both manufacturers of DBS systems, consulting fees by Newronika and CereGate and honoraria for lecturing by Abbott. JH was a consultant for Neuralink and serves on the Medical Advisory Board of Enspire DBS. SS was a consultant for Boston Scientific, Zimmer Biomet, NeuroPace, Koh Young, and is a co-founder of Motif Neurotech. RSR was employed by Medtronic Inc. MM was employed by Boston Scientific Neuromodulation Corporation. DG was employed by NeuroPace, Inc. LK, MA, LR, SMa, and AP were employed by Newronika. RG was employed by Rune Labs.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Hematoma-induced Twiddler-like phenomenon as a presentation of DBS hardware failure: Case report

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Deep brain stimulators (DBS) may fail for a multitude of reasons. We present a 79-year-old Parkinson's disease patient who suffered a DBS failure following impulse generator (IPG) replacement surgery due to the IPG flipping within an expanded capsular pocket. This creation of the pocket was unintentional, and the pocket formed around an undiagnosed postoperative hemorrhage. The syndrome could be considered "Twiddler-like" because it resulted in device flipping. There were, however, many characteristic differences between our case and classical Twiddler's syndrome. DBS neurostimulator failure due to hematoma induced device flipping should be suspected when device interrogation is impossible or there are abnormally high impedances across multiple DBS lead contacts. A plain film X-ray series should be ordered and can be useful in providing radiological evidence of device flipping. In cases like ours the extensive braiding encountered in Twiddler's syndrome may be absent. Anchoring the IPG to a deep fascial layer as well as the use of an antimicrobial pouch are two methods that may be employed to prevent or to treat this complication.

KEYWORDS

deep brain stimulation, Twiddler's syndrome, neurostimulator failure, pocket hematoma, impulse generator

Introduction

A deep brain stimulator (DBS) device consists of an intracranially placed lead, a subcutaneous extension wire, and implantable pulse generator (IPG). The IPG is most commonly placed in the subclavicular location. A minority of patients will undergo IPG placement in an abdominal location. The clinician must be able to connect and to facilitate communication with the device through a handheld programmer in order to pursue device maintenance and programming. In the case of a rechargeable device, the patient must be able to connect to the device to enable the wireless charging function. If the device flips over, it may not be accessible for programming or for charging. We report an unusual case of neurostimulator device failure due to "flipping" over in an expanded subcutaneous capsular pocket that formed around an undiagnosed postoperative hematoma.

Case report

A 79-year-old woman with advanced Parkinson's disease (PD) and BMI of 32.3 presented for troubleshooting of her DBS device. Her first symptom of PD was a right upper extremity tremor. As her disease progressed, she developed worsening tremor in both upper extremities, dystonia, and cramping of the right foot. She also progressed to develop motor fluctuations, severe bradykinesia, and dyskinesias. She did not have any significant psychiatric co-morbidities such as obsessive compulsive disorder. Significant dementia was not identified on neuropsychological screening and she was deemed a good candidate for DBS. The patient did not have any history of bleeding diathesis and was not taking any antiplatelet or anticoagulation medications. She underwent bilateral globus pallidus interna (GPi) DBS implantation without complication and the IPG (non-rechargeable) was placed in her abdomen which was her preference for cosmesis. During elective replacement of the IPG for battery depletion she requested placement of a rechargeable neurostimulator. Prior to replacement, the patient had not experienced any recent weight loss. A new, more superficial, pocket for the device was created to accommodate charging. The device was tested intraoperatively and found to have normal impedances and full wireless pairing with the external charging device was confirmed. The device was anchored to the underlying tissue with 2-0 silk at the two anchoring sites in the standard fashion.

One month following the neurostimulator replacement surgery, the patient alerted the clinic that she had (for a week) been unable to communicate with or charge her device. During evaluation in clinic the device could not be interrogated, and programming was not possible. There were no abnormal physical exam findings. Plain film X-rays revealed the IPG had flipped 180° along its long axis (see Figure 1). Upon palpation of pulse generator site, we were unable to manually induce a flip of the device. The patient returned to the surgical suite that week where upon exploration of the IPG pocket, a large brown liquefied hematoma was observed. Following drainage, a large capsule was encountered. The IPG was restored to the correct orientation and replaced in a revised pocket, which was made smaller, and the IPG was anchored to the anterior abdominal wall with 2-0 silk at both anchoring sites on the IPG. Intraoperative interrogation of the device demonstrated normal functioning. Subsequent discussion with the patient revealed that there was swelling at the surgical site several days following the IPG replacement surgery, but denied any significant bruising. However, she did not seek care for the swelling until there was a failure to charge the device. Additionally, the patient could not recall any trauma to the abdomen or surgical site following the index operation prior to revision surgery. Six months after the intervention, the patient continued to be able to interrogate and charge her device and was receiving good therapeutic benefit from the system.

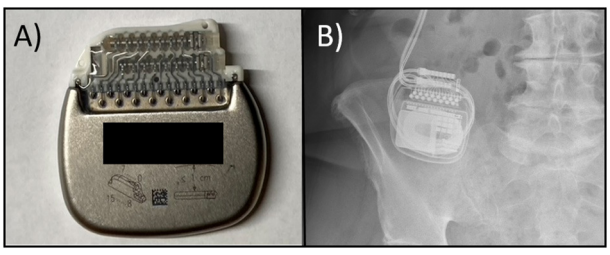

FIGURE 1
(A) Photo of a rechargeable IPG with the expected normal positioning of the DBS leads which exit to the right of the device; the device label is noted to have an upward orientation with the manufacturing label intentionally obscured, **(B)** A plain film X-ray series from our case demonstrating the abnormal insertion of the leads on the left side suggestive of flipping.

Discussion

We observed a rare pocket hematoma resulting in neurostimulator (IPG) flipping with device failure. This complication manifested with an inability of the patient to recharge her device. We hypothesize that hemorrhage created an acute gelatinous hematoma that locked the IPG in a partially flipped position, facilitating formation of a fibrous capsule around the IPG and hematoma. The evolution into a chronic liquid hematoma likely allowed the IPG to mobilize within the enlarged capsule, rotate, and then become lodged in a suboptimal position for device communication, charging, and programming. Figure 2 provides a summary of the events likely leading to device failure. One could also speculate that the device became mobile following surgery, flipped, and initiated a slow bleed leading to a hematoma and enlarged pulse generator capsule. This would result in a similar situation of hypermobility, flipping of the device, and ultimately device failure due to an inability to charge or program the device once settled in the inappropriate position. Both the abdominal placement of the IPG and the patient's obese BMI of 32.3 put her at risk for this to occur (Burdick et al., 2010).

This phenomenon resembles Twiddler's syndrome (TS), however based on its characteristics it would not qualify for this diagnosis. First reported in 1968, shortly after the introduction of implantable pacemakers (Bayliss et al., 1968), TS is a rare complication caused by repeated flipping of the neurostimulator within the implanted pocket. Traditionally, TS flipping due to the unintentional manipulating or picking of the device (i.e., "twiddling"). The estimated TS prevalence in cardiac pacemakers is 1% of all implantation malfunctions (Hill, 1987). In neurostimulation, TS has been estimated to account for 1.3% of all DBS malfunctions (Burdick et al., 2010). TS has been demonstrated in the spinal cord stimulation (Son et al., 2018) and the vagal nerve stimulation literature (Trout et al., 2013). Risk factors for TS include surgical technique, unconscious flipping of the device by the patient (Menghetti et al., 2014), obese body habitus (Femenia et al., 2010), early return to exercise (Bracke et al., 2005), and the shape of the device (Gul et al., 2017). Obsessive compulsive symptoms may also contribute and the TS patient may not be conscious that they are flipping the device (Femenia et al., 2010; Moliz et al., 2015). It has been postulated that the abdominal pulse generator location, as was the location in our patient, may be more prone to flipping then the chest site (Boyle et al., 1998; Burdick et al., 2010; Gelabert-Gonzalez et al., 2010). Given the many potential reasons that

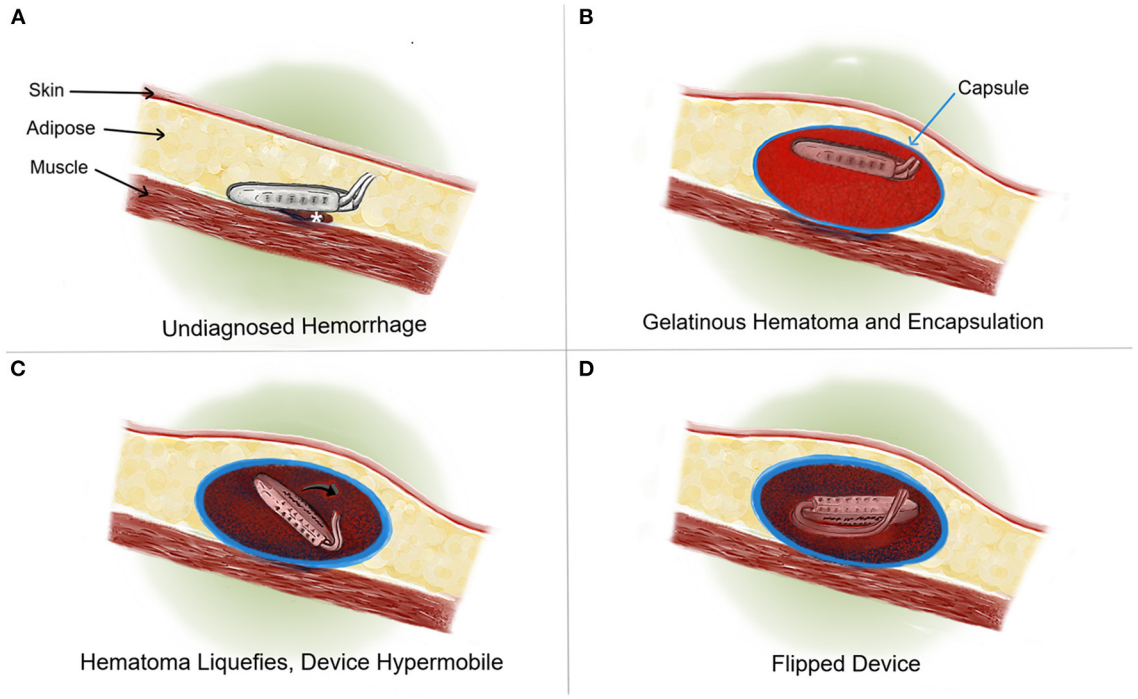

FIGURE 2
Cross sectional rostral to caudal view medical illustration. **(A)** An example of an IPG implanted with a resulting bleed (*). **(B)** Formation of a solid, gelatinous clot which expands until cessation of bleeding. A fibrous capsule is formed around the IPG and clot over the course of several weeks. At this time the IPG remains in appropriate orientation that facilitates interrogation and charging. **(C)** Over time, the blood clot evolves, breaking down into liquid blood. This scenario results in the hypermobility of the IPG (→) within a now enlarged and well-formed capsule. **(D)** The hypermobile IPG is "flipped" and cannot be charged by the patient or programmed by the clinician.

could lead to device hypermobility, flipping, and failure, we believe the field should evaluate the use of the term TS to describe this phenomenon.

The repetitive flipping of the devices usually presents as a loss of benefit. It may lead to hardware failure, often associated with out-of-range elevated impedances discovered to be present across all electrode contacts (open-circuit), and potentially associated with an inability to communicate with or to charge the device. TS can result in lead fracture or migration. Although the flipping occurs in the pocket, the lead damage is often rostral to the IPG and may be in the nuchal region. Though our case may not be due to twiddling, as our patient denied any manipulation of the device after surgery, the result of the single flip in orientation due to a hematoma resulted in Twiddler-like manifestations.

The workup for device flipping or TS includes interrogation of the device, specifically searching for an open or short circuit, as well as obtaining plain film X-rays. The imaging usually reveals an inappropriate position of the neurostimulator that "flipped" along the long axis (see Figure 1). The electrical leads may be dislodged or displaced and there may possibly be twisting or braiding of the extension wire although any braiding or twisting is usually minimal as the device usually flips only once and at the rotation is 180 degrees or less. Prevention and treatment are similar with the goal of firmly securing the neurostimulator within the device pocket. Anchoring the IPG to a strong fascial layer with a non-absorbable suture has been recommended (Sobstyl et al., 2017). An antimicrobial pouch can also be used to decrease IPG mobility (Osoro et al., 2018). The pouch is thought to manifest its effectiveness by occupying more space in the pocket, and thus inducing a more robust inflammatory response. It may also work through increasing friction between the IPG-surface and the surrounding tissue (Shandling et al., 1991; Osoro et al., 2018).

This report demonstrates a previously undescribed and unusual presentation of device failure due to a postoperative implantation hematoma and expanded capsule. Prior literature demonstrates that all neurostimulator systems retain the risk for device flipping or patient twiddling leading to device failure. A strength of this report is our presentation of mitigation techniques to prevent this complication. While we are limited to our timepoints of evaluation in this case, as we did not have the opportunity to evaluate the patient when she noted the swelling, we were able to observe the consequences of this with the expanded device capsule.

Conclusion

In conclusion, we report a novel cause for IPG flipping. It is unknown whether this complication will be more common in the abdominal or subclavicular IPG location and future reports may help to clarify this point. Utilizing a technique to reduce mobility of the neurostimulator may reduce this potential complication.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MH, AA-G, MO, and KF conceptualized the study. MH and AA-G gathered the data. MH wrote the first draft of the study. All authors provided crucial input about the study, critically evaluated, edited, and approved the final version of the manuscript.

Conflict of interest

MO serves as a consultant for the Parkinson's Foundation and has received research grants from NIH, Parkinson's Foundation, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. MO's DBS research was supported by: NIH R01 NR014852 and R01NS096008. MO is PI of the NIH R25NS108939 Training Grant. MO has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, Perseus, Robert Rose, Oxford, and Cambridge (movement disorders books). MO is an associate editor for New England Journal of Medicine Journal Watch Neurology. MO has participated in CME and educational activities on movement disorders sponsored by the Academy for Healthcare Learning, PeerView, Prime, QuantiaMD, WebMD/Medscape, Medicus, MedNet, Einstein, MedNet, Henry Stewart, American Academy of Neurology, Movement Disorders Society, and by Vanderbilt University. The institution and not MO receives grants from Medtronic, Abbvie, Boston Scientific, Abbott, and Allergan and the PI has no financial interest in these grants. MO has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria. Research projects at the University of Florida receive device and drug donations. LA has worked as an educational consultant and has participated in advisory board, therefore receiving honoraria for his activities, for Medtronic and Boston Scientific. WD has received training grant funding from the Tourette Association of America, American Brain Foundation, and Dystonia Medical Research Foundation. He received royalties for publication from Robert Rose, Inc. He received honoraria for a consultation for Medtronic, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1160237/full#supplementary-material

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Time-locked acute alpha-frequency stimulation of subthalamic nuclei during the evaluation of emotional stimuli and its effect on power modulation

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Introduction: Deep brain stimulation (DBS) studies in Parkinson's Disease (PD) targeting the subthalamic nucleus (STN) have characterized its spectral properties across cognitive processes. In emotional evaluation tasks, specific alpha frequency (8–12 Hz) event-related de-synchronization (ERD) (reduced power) has been demonstrated. The time-locked stimulation of STN relative to stimuli onset has shown subjective positive valence shifts with 10 Hz but not with 130 Hz. However, neurophysiological effects of stimulation on power modulation have not been investigated. We aim to investigate effects of acute stimulation of the right STN on concurrent power modulation in the contralateral STN and frontal scalp EEG. From our previous study, we had a strong *a priori* hypothesis that negative imagery without stimulation would be associated with alpha ERD; negative imagery with 130 Hz stimulation would be also associated with alpha ERD given the lack of its effect on subjective valence ratings; negative imagery with 10 Hz stimulation was to be associated with enhanced alpha power given the shift in behavioral valence ratings.

Methods: Twenty-four subjects with STN DBS underwent emotional picture-viewing tasks comprising neutral and negative pictures. In a subset of these subjects, the negative images were associated with time-locked acute stimulation at either 10 or 130 Hz. Power of signals was estimated relative to the baseline and subjected to non-parametric statistical testing.

Results: As hypothesized, in 130 Hz stimulation condition, we show a decrease in alpha power to negative vs. neutral images irrespective of stimulation. In contrast, this alpha power decrease was no longer evident in the negative 10 Hz stimulation condition consistent with a predicted increase in alpha power. Greater beta power in the 10 Hz stimulation condition along with correlations between beta power across the 10 Hz stimulation and unstimulated conditions suggest physiological and cognitive generalization effects.

Conclusion: Acute alpha-specific frequency stimulation presumably was associated with a loss of this expected decrease or desynchronization in alpha power to negative images suggesting the capacity to facilitate the synchronization

of alpha and enhance power. Acute time-locked stimulation has the potential to provide causal insights into the spectral frequencies and temporal dynamics of emotional processing.

KEYWORDS

deep brain stimulation (DBS), acute stimulation, alpha frequency, emotion, event related (de)/synchronization

Introduction

Deep brain stimulation (DBS) is a neurosurgical procedure that involves targeted implantation of electrodes to deliver electrical pulses (Benabid et al., 2009; Lozano et al., 2019). Randomized controlled trials have shown DBS efficacy for neurological disorders such as Parkinson's disease (PD) (Benabid et al., 2009) and for psychiatric disorders such as obsessive-compulsive disorder (OCD) (Blomstedt et al., 2013; Visser-Vandewalle et al., 2022). For PD, high-frequency (e.g., 130 Hz) subthalamic nucleus (STN) stimulation is commonly used clinically to relieve motor symptoms (Benabid et al., 2009), while lower frequencies (e.g., 60 Hz) are used to target gait symptoms (Xie et al., 2017). The STN, a nucleus found in the indirect pathway of basal ganglia, receives both indirect and hyperdirect projections from the cortico-striatal-thalamo-cortical circuitry with evidence for both segregation as well as integration of motor, cognitive, and limbic substrates (Kim et al., 2015; Eisinger et al., 2019).

Complementary to the clinical benefits, DBS studies targeting the STN for PD have contributed greatly to our understanding of the STN circuits (Eisinger et al., 2019). STN recordings acquired under various task paradigms also provide knowledge on the functional role of STN in cognition and emotion. For instance, spectral dynamics of STN response in emotional evaluation tasks have demonstrated specific event-related de-synchronization (ERD) or reduced activity in the alpha frequencies (8–12 Hz) with latency nearly 0.5 s after image onset and peaking at 1–2 s (Kühn et al., 2005a; Brücke et al., 2007; Huebl et al., 2011, 2014; Buot et al., 2013). This ERD correlates with subjective emotional valence ratings (Brücke et al., 2007) and also is associated with depressive symptoms (Huebl et al., 2011). Consistent and supporting evidence about the role of alpha ERD in emotional processing also comes from other DBS studies targeting other subcortical structures such as the habenula (Sonkusare et al., 2022a). Furthermore, chronic high-frequency STN stimulation in PD enhances positive valence bias (Irmen et al., 2017), and chronic anteroventral STN stimulation in patients with obsessive-compulsive disorder enhanced the positive ratings of low-intensity negative and positive images (Voon et al., 2017). Thus, a multitude of studies implicates the involvement of STN neural oscillations, especially in the alpha band, in emotional processing.

DBS studies also offer the potential for acute stimulation which can be time locked according to the presentation of stimuli. Such refined methods of stimulation which explore the timing of stimulation delivery and its effect on subjective evaluation provide causal insights about the spectral frequencies and temporal dynamics of emotional processing as well as potential development of neuromodulation protocols. In our previous study, we specifically addressed this question showing that acute one-second alpha-specific (10 Hz) frequency stimulation of the STN time-locked to the evaluative period of affective negative imagery enhances subjective positive emotional subjective valence but not with acute clinical high-frequency (130 Hz) stimulation (Mandali et al., 2021). The effect of stimuli-locked stimulation on subjective behavioral ratings was investigated, and neurophysiological effects of stimulation were not reported. Electrodes for DBS allow either stimulation or recordings at one time but never concomitantly. In the previous study, we had stimulated right STN, while recordings from left STN but data were not analyzed. In this study, in a complementary analysis, we aimed to investigate the effect of stimulation on concurrent power modulation of the left STN neural activity. Based on our previous behavioral findings of stimulation, we had a strong *a priori* hypothesis that negative imagery without stimulation would be associated with alpha ERD and negative imagery with 130 Hz stimulation was also associated with alpha ERD given the lack of effect on behavioral subjective valence ratings. We further hypothesized that 10 Hz stimulation would facilitate or enhance alpha power during negative imagery given the shift in behavioral valence ratings.

Materials and methods

Twenty four PD patients participated in the study: six females, age (mean ± SD) = 59.71 ± 11.84, right-handed, BDI-II = 12.54 ± 7.18. Detailed information on the recruitment criterion, patient demographics, clinical evaluation, surgical procedures, and stimulation parameters including settings and protocol are provided in the previous study (Mandali et al., 2021). All procedures utilized in the current study were approved by the ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Electrode localization

The intended target coordinates of the subthalamic nucleus (STN) were determined by integrating post-operative computed

Abbreviations: DBS, Deep Brain Stimulation; STN, Subthalamic Nucleus; PD, Parkinson's Disease; OCD, Obsessive-Compulsive disorder; ERD, Event Related De-synchronization; LFP, Local Field Potential; LPR, Log of the Power Ratio.

tomography and pre-operative 3.0 Tesla magnetic resonance imaging (MRI) images within Surgiplan software (Elekta, Sweden). Quadripolar electrodes with four platinum–iridium contacts (Medtronic 3387S, Medtronic, USA; or PINS L302, PINS, China; Sceneray SR1210, China) were implanted using stereotactic navigation into the bilateral STN under general anesthesia. Participants were tested 24 h after surgery to avoid the stun effect and at least 30 min after their regular medication dose. Post-operative CT and pre-operative T1 MRI were used to reconstruct the electrode trajectories and their locations by employing the LEAD-DBS toolbox (Deiber et al., 2020) (Figure 1). Briefly, a two-stage linear registration as implemented in using Advanced Normalization Tools (ANT) (Campbell et al., 2012) was used, and the post-operative CT co-registered to pre-operative MRI and spatially normalized into MNI_ICBM_2009b_NLIN_ASYM space (Sonkusare et al., 2022a). The Pacers algorithm (Sonkusare et al., 2022b) was used to localize electrodes in MNI space.

Paradigm

Subjects completed 90 trials of each of the emotional picture-viewing tasks (Figure 2A), utilizing pictures from the International Affective Picture System (IAPS) (Lang et al., 1997). Two tasks were run associated with either 10 or 130 Hz stimulation randomized across 2 separate days. The stimuli comprised three conditions displayed for 2.5 s randomly presented negative images associated with time-locked acute stimulation of either 10 or 130 Hz, negative images without stimulation, and neutral images without stimulation. A fixation cross was prefixed to the image presentation, the duration of which was jittered (1–1.5 s). For the stimulation-associated images, 1 s stimulation began at 0.2 s after the image, hence ending at 1.2 s after image onset. The stimulation onset was designed at delayed onset after image onset to avoid interference with early visual processing (Olofsson et al., 2008). Five images per category in each task were rated for valence and arousal (Figure 2B). Subjects were blind to the stimulation condition, and the presentation of the images with stimulation was randomized. Further details of the task paradigm are available in our previous study (Mandali et al., 2021).

The IAPS rating of stimuli within two negative conditions (with and without stimulations) for each of the two tasks was matched. IAPS ratings of stimuli in three conditions of each task are 10 Hz task negative with stimulation (valence: 2.26 $\pm$ 0.4, arousal: 5.81 $\pm$ 1.1), negative (valence: 2.46 $\pm$ 0.48, arousal: 5.85 $\pm$ 0.74), and neutral (valence: 5.03 $\pm$ 0.32, arousal: 3.1 $\pm$ 0.68) and 130 Hz task negative with stimulation (valence: 2.53 $\pm$ 0.58, arousal: 5.7 $\pm$ 0.7), negative (valence: 2.38 $\pm$ 0.45, arousal: 5.55 $\pm$ 0.77), and neutral (valence: 5.1$\pm$ 0.38, arousal: 3.2 $\pm$ 0.63).

Data acquisition

Patients were comfortably seated at a distance of 75 cm in front of a computer screen (LG, model L1954, 30 $\times$ 38 cm) with their right hand on a mouse to rate the images on visual analog scales. The experiment was coded in Psych toolbox 3 and run on MATLAB 2017 (The MathWorks, Natick, MA, USA) environment utilizing a Windows 7 desktop (Dell, Texas, USA). The local field potentials (LFP) and scalp electro-encephalogram (EEG) were recorded simultaneously using a BrainAmp MR amplifier (Brain Products, Gilching, Germany) at 500 Hz sampling rate employing a notch filter to remove 50 Hz power line interference. Intermittent stimulation was delivered *via* middle contacts of the right-STN (R1 anode and R2 cathode whereas R0 is ventral and R3 is dorsal) for 1 s at either 130 Hz or 10 Hz. The contact placement is reported in the previous publication (Mandali et al., 2021). The current pulses were delivered using a pulse generator (Scene Ray, model 1510, Suzhou, China) approved by the National Medical Products Administration, China. The precise time-based control of turning "ON" and "OFF" the stimulator was programmed within the experimental paradigm run on MATLAB, interfaced *via* a parallel port. Since the right STN was stimulated, a concurrent recording was acquired from the left STN contacts (L0, L1, L2, and L3) which were used for analyses in this study. The scalp EEG data were collected from seven frontal electrodes (Fp1, Fp2, F3, F4, F7, F8, and Fz) using the 10–20 placement system and the left mastoid as the reference channel.

Data pre-processing

The raw data were subjected to re-referencing, filtering, trial extraction, and artifact corrections. First, the LFP data were re-referenced using a bipolar montage: subtracting data between adjacent contact pairs (e.g., L0–L1, L1–L2, and L2–L3) to extract three new LFP signals (henceforth to be referred as L_v-ventral, L_m-middle, and L_d-dorsal, respectively). The aim was to mitigate volume conduction (Nunez and Cutillo, 1995). Next, a 1-Hz high-pass Butterworth filter was employed to remove potential DC offset from the extracted signals. Subsequently, trials corresponding to each condition were extracted. For analysis, the 1 s pre-stimulus baseline and the last 1.1 s of the trial period following stimulation were considered for the subsequent analysis, excluding 0.2 s after stimulation offset as a precaution for a possible contamination and rebound effect. The epoched trials were concatenated to form input signals for further processing. Finally, independent component analysis (Infomax ICA) was employed on those input signals to maximally separate similar signals and noise into separate components (Amari et al., 1995; Muhammad, 2008). Following Tukey (1977) extreme outlier samples (absolute values), three inter-quartile ranges away from the third quartile were removed from each ICs (and replaced with zeros) after pre-correcting for skewness by employing "medcouple" measure as described previously (Brys et al., 2004). The ICs were then projected back (multiplying processed ICA signals with the inverse of the un-mixing matrix) to the original signal space furnishing markedly cleaner bipolar LFP signals. Scalp EEG data were also pre-processed in a similar manner as LFP data albeit with some differences. Specifically, re-referencing involved slight variations: five bipolar EEG signals were extracted by subtracting anterior-posterior and left-right

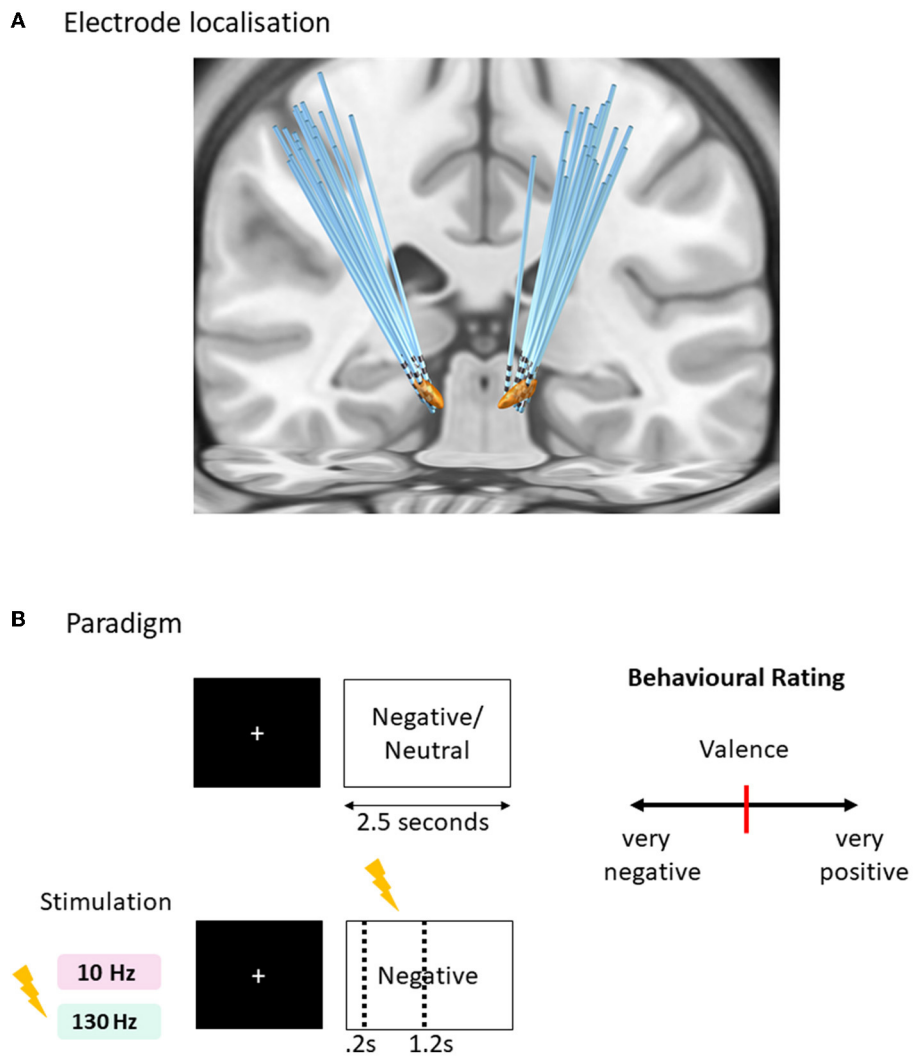

FIGURE 1
Affective task paradigm with acute time-locked stimulation. **(A)** Sequence of a typical trial in three conditions of tasks (negative and neutral without stimulation, negative with stimulation). One of the negative condition was paired with acute right subthalamic nuclei stimulation for 1 s duration after 0.2 s of the image onset lasting for 1 s, within the 2.5 s duration of the trial. Two versions of the task were created with matching valence and arousal values tested in randomized order with 130 Hz and 10 Hz stimulation frequencies. **(B)** Rating design displaying a question to score the behavioral measure of valence and arousal on a visual analog scale [ranges from 0 to 100 with initial position fixed at 50 (red bar in the center)] using the mouse. Each trial is separated with an inter-trial interval jittered between 1 and 1.5 s with a fixation cross displayed at the center of the screen.

adjacent electrode pairs (F7–F3, F3–Fz, FP1–FP2, Fz–F4, and F4–F8) for further processing (henceforth referred as E1, E2, E3, E4, and E5, respectively).

Power features

To compute power spectrum for trials of each subject, segments (baseline and three task conditions separately) of the epoched LFP and scalp EEG time series were tapered by employing a Hann window, zero padded (ten times the length of the segment) with 50% overlap for the purpose of smoothing and mitigating edge effects to estimate average spectra (*pwelch* function in Matlab). The *welch* method was employed for improved signal-to-noise ratio, especially in the presence of non-stationarities which may arise due to segmentations of time series. The average power of baseline and task conditions were estimated in *delta* (D: 2–4 Hz), *theta* (T: 4–8 Hz), *alpha* (A: 8–12 Hz), *beta* (B: 12–30 Hz), *gamma* (G: 30–60 Hz), and high *gamma* (HG: 60–200 Hz) frequency bands. For each experiment, the suppression or enhancement of power (in specific bands) of task conditions was estimated relative to the baseline as the log of the power ratio (LPR) (Pineda and Hecht, 2009).

Non-parametric statistical analysis

The task conditions in the experiment were neutral (neu), negative (neg), negative 10 Hz stimulation (neg10), and negative

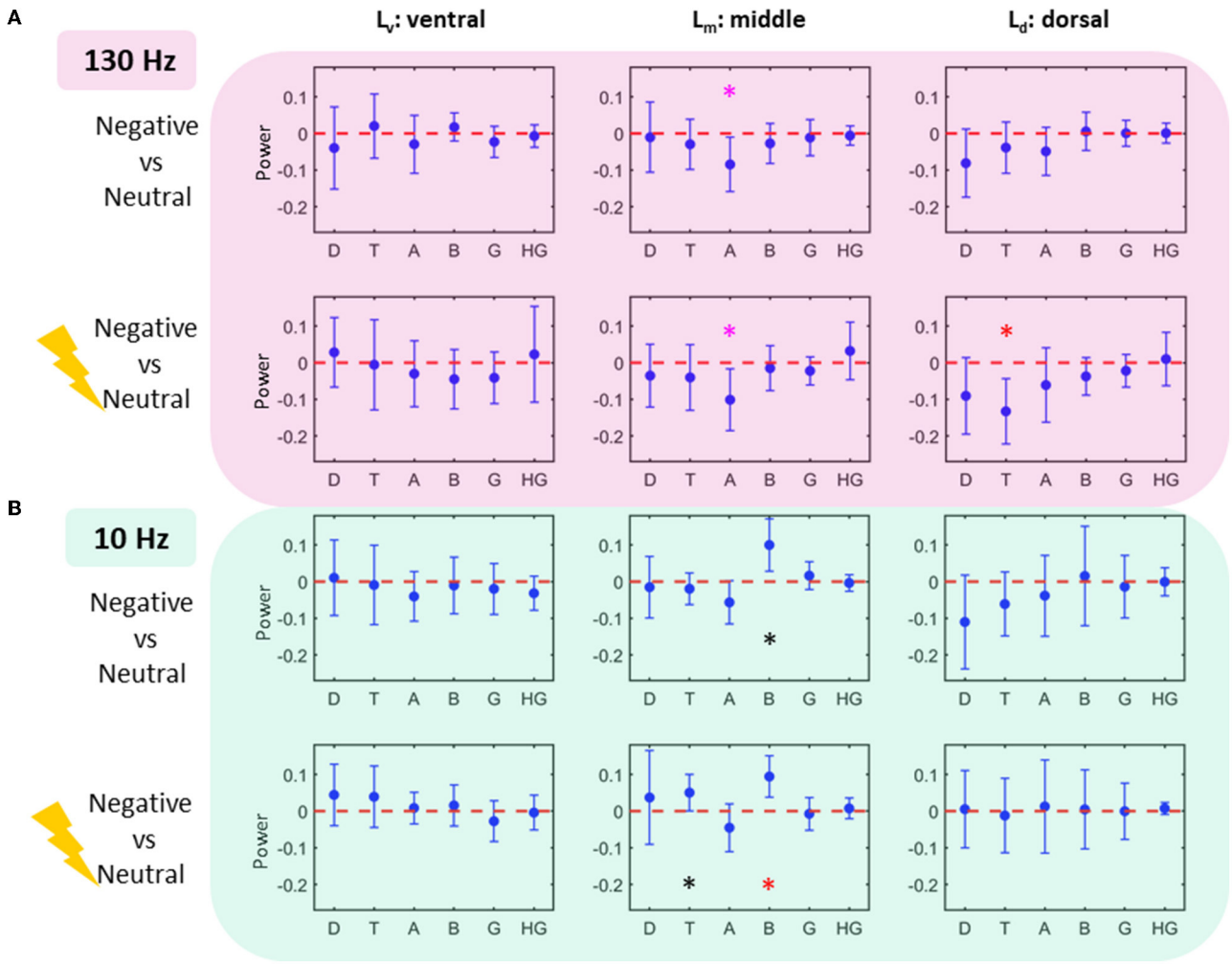

FIGURE 2
Power modulations as calculated with log-to-power ratio (LPR) **(A)** *130 Hz Stimulation Task:* Middle contact L_m depicts alpha power decrease for both LPR_{neg} vs. LPR_{neu} and LPR_{neg130} vs. LPR_{neu} comparisons consistent with *a priori* hypotheses ($p < 0.05$). L_d also shows theta decrease for LPR_{neg10} vs. LPR_{neu} comparison ($p < 0.05$, corrected). **(B)** *10 Hz Stimulation Task:* Middle contact L_m depicts beta increase for both LPR_{neg} vs. LPR_{neu} ($p < 0.05$; uncorrected; black star) and LPR_{neg10} vs. LPR_{neu} comparisons ($p < 0.05$; corrected; red star). Lm also shows theta increase for LPR_{neg10} vs. LPR_{neu} comparison ($p < 0.05$; uncorrected). Note that the middle contact L_m was not associated with alpha decrease for LPR_{neg10} vs. LPR_{neu} comparisons which is consistent with an increase in alpha power by decreasing the alpha desynchronization effect. Uncorrected significance is denoted by a black star and significance withstanding multiple comparisons corrections ($p < 0.05$) is denoted by a red star. Significance testing for *a priori* hypotheses is shown in a mauve star. Error bars denote standard deviation.

130 Hz stimulation (neg130). The LPR of each active condition was defined as LPR_{neg}, LPR_{neg10}, LPR_{neg130}, and LPR_{neu}. Statistical comparisons were employed between LPRs of negative (including stimulation) conditions vs. neutral conditions. To correct for multiple comparison corrections, the permutation method was employed to protect against false rejection of the null hypothesis: *no difference across LPR features of conditions*, at probability $\alpha = 0.05$. More specifically, data were randomly permuted across all possible pairs of LPR features extracted from conditions (within each contact and band) in the task and the experiment, and test statistics (t-value) was calculated. This procedure was repeated 1,000 times and the maximum absolute t-value was retained for each permutation. The p-value was estimated by the proportion that resulted in a larger test statistic than the original non-permuted observed one (Maris and Oostenveld, 2007).

Results

Comparison of STN power features

130-Hz stimulation task

In keeping with our *a priori* hypotheses, the middle contact L_m showed an alpha power decrease in both LPR_{neg} vs. LPR_{neu} in the unstimulated condition and LPR_{neg130} vs. LPR_{neu} comparisons in the 130 Hz stimulated condition ($p < 0.05$) (Figure 2). The dorsal contact L_d showed a trend toward a theta decrease ($p < 0.05$; uncorrected) only in the case of stimulated negative condition.

10 Hz stimulation task

Critically, with stimulation at 10 Hz, LPR_{neg10} vs. LPR_{neu} comparison of the middle contact no longer showed an alpha

power decrease suggesting that acute 10 Hz stimulation enhanced alpha power, thus eliminating the expected alpha ERD, as predicted. The beta frequency power of the middle contact L_m showed LPR_{neg} vs. LPR_{neu} that showed a trend toward an increase in the unstimulated condition ($p < 0.05$; uncorrected), whereas corresponding comparison in stimulated negative condition (LPR_{neg10} vs. LPR_{neu}) showed a theta increase ($p < 0.05$; uncorrected) as well as beta increase ($p < 0.05$; uncorrected). After multiple comparison corrections for findings that did not have a specific *a priori* hypothesis, only the beta increase in the stimulated negative condition at 10 Hz remained significant ($p < 0.05$).

Comparison of scalp EEG power features

Figure 3 shows comparisons of scalp EEG LPR features extracted from the conditions in two tasks. Comparisons were statistically tested for effects only at theta, alpha, and beta bands (where significance was already established for LFP data) at five bipolar electrodes. All the effects were found in LPR comparison of stimulated negative condition to neutral in 10 Hz stimulation task: beta increases were found at E_2 and E_5 ($p < 0.05$; uncorrected), whereas a theta increase was located at E_3 ($p < 0.05$; uncorrected).

Power interaction across frequency bands and STN contacts

Following the results represented in Figure 2, a regression analysis was conducted across pairs of bands, each as a function of locations and negative affect conditions (Figure 4). For the 130 Hz stim task, the following relationships were sought: *theta* (Lr, LPR_{neg130}) vs. *alpha* (Lm, LPR_{neg130}), *theta* (Ld, LPR_{neg130}) vs. *alpha* (Lm, LPR_{neg}), and *alpha* (Lm, LPR_{neg130}) vs. *alpha* (Lm, LPR_{neg}). Only *beta* (Lm, LPR_{neg10}) vs. *beta* (Lm, LPR_{neg}) for 10 Hz stimulation tasks showed a significant relationship even after multiple comparison corrections. For the 10 Hz stim task, the following relationships were sought: *theta* (Lm, LPR_{neg10}) vs. *beta* (Lm, LPR_{neg10}), *theta* (Lm, LPR_{neg10}) vs. *beta* (Lm, LPR_{neg}), and *beta* (Lm, LPR_{neg10}) vs. *beta* (Lm, LPR_{neg}).

Discussion

Our findings highlight the role of acute one-second right STN stimulation at 10 and 130 Hz on power modulations of contralateral STN LFP recordings during the subjective evaluation of negative imagery. We previously reported the effects of stimulation on subjective valence showing a shift toward positive subjective valence with 10 Hz stimulation but not 130 Hz stimulation (Mandali et al., 2021) and, in this study, investigated the physiological effects.

As hypothesized, in the 130 Hz stimulation condition, we show a decrease in alpha power to negative vs. neutral images irrespective of stimulation. This is consistent with previous findings in the literature of STN LFP recordings of a decrease in alpha power, or desynchronization, to affectively valenced images without stimulation (Huebl et al., 2014; Schubring and Schupp, 2019). This is also consistent with our demonstration of the lack of effect of acute high-frequency stimulation at 130 Hz on subjective valence as we previously reported (Mandali et al., 2021). We further show that acute alpha-specific frequency stimulation presumably was associated with a loss of this expected decrease or desynchronization in alpha power to negative images suggesting the capacity to facilitate the synchronization of alpha and enhance power. Additionally, we also observed enhanced synchronization in the frequency adjacent to that being stimulated with enhanced *beta* power, bands above that being stimulated, but not in more distant frequencies such as *delta* or *gamma*. This effect was also observed in a trend increase in prefrontal scalp EEG theta and beta bands. This physiological generalization may be related to the nature of our stimulation which was time-locked to a cognitive task but not phase-locked to the individual's specific frequency which may be associated with greater specificity as shown for treating tremors in PD (Little et al., 2013; Cagnan et al., 2017).

We further show a significant correlation in beta power to negative images across both the stimulated and unstimulated conditions along with a trend increase (p uncorrected) in beta power to negative images without stimulation within the alpha stimulation condition. These findings were not observed in neutral images or within the 130 Hz stimulation condition. This highlights a potential cognitive generalization effect that might reflect a generalization of a learned association between stimulation and negative valenced imagery. Acute alpha stimulation of negative imagery appears to enhance adjacent beta power to not only stimulated negative imagery but also other unstimulated negative imagery but critically and not to neutral stimuli. This suggests a potential learned association between negative imagery and 10 Hz stimulation on a physiological measure that then generalizes to imagery with similar negatively valenced features but not to neutral valenced features.

The duration of stimulation may lead to varied stimulation effects. For instance, local firing rates of neurons have been shown to increase after short bursts of high-frequency STN stimulation but are suppressed with prolonged stimulation (Lee et al., 2009). These observations may be more specific to high-frequency stimulation. In this study, we contrasted acute stimulation of similar short 1-s duration with differing frequencies and suggest our findings are frequency specific.

The role of the alpha ERD in subjective valence requires further investigations, and in this study, it was not specifically addressed. Alpha activity is most prevalent during resting wakefulness with closed eyes and decreases with enhanced attentional states. Modulation of alpha power with neurofeedback has been shown to modulate attention (Bagherzadeh et al., 2020; Deiber et al., 2020). Decreasing attention specifically toward negative imagery might also decrease the cognitive evaluation of subjective valence.

Current stimulation protocols for PD use high-frequency clinical stimulation of 130 or 160 Hz. Although this leads to dramatic reductions of motor symptoms, affective symptoms may linger (Campbell et al., 2012). Our results open up various avenues to tackle these mood symptoms. For instance, acute stimulation protocols could be paired up with neurofeedback training to modify emotional dysfunction not just in PD but

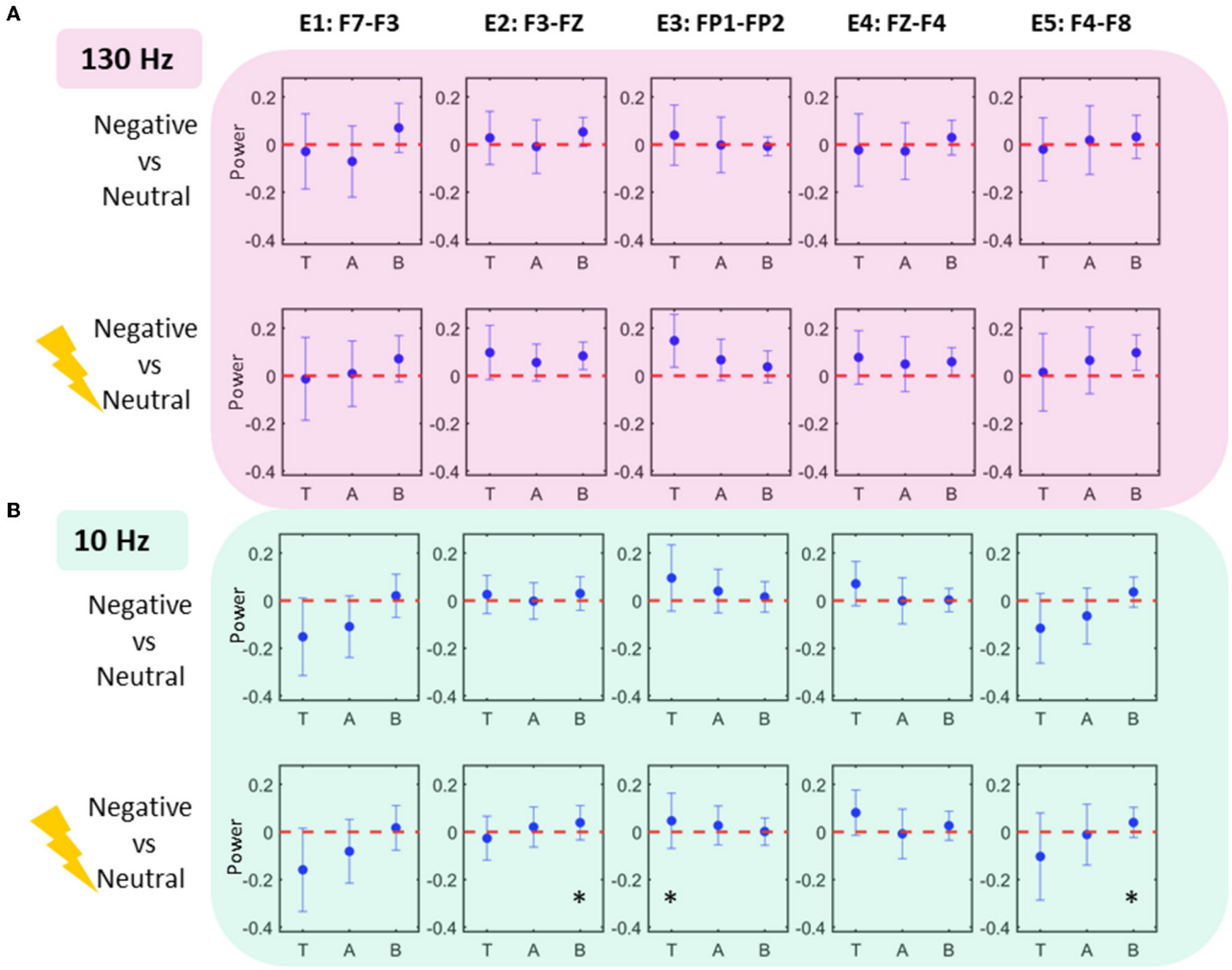

FIGURE 3
Scalp EEG power modulations. Each column shows the scalp EEG electrode power modulations in 10 Hz condition **(A)** and 130 Hz condition **(B)**. Effects (significance uncorrected) are seen in 10 Hz task at electrodes E2, E3, and E5 showing an increase in theta and beta power.

other affective disorders amenable to DBS such as depression and obsessive-compulsive disorder. For example, DBS of habenula has shown promise for treating depression and alpha signatures to be correlated with depression severity (Sonkusare et al., 2022a) or dynamics of amygdala-prefrontal cortex circuitry in emotion processing (Sonkusare et al., 2022b) which can be targeted for neurofeedback training.

This study has some limitations. We stimulated the right STN but recorded it from the left STN as we were unable to stimulate and record from the same contacts. We did not analyze physiological data during the stimulation itself or 0.2 seconds immediately after stimulation end to avoid stimulation artifact and rebound effects although it remains plausible that our findings may still be contaminated by rebound or withdrawal effects rather than a specific role of stimulation influencing synchronization. Although newer methods for stimulation artifacts removal have been developed (Dastin-van Rijn et al., 2010), it is not a trivial issue. Future studies can build on our study to implement and validate artifact removal techniques. Additionally, the data were acquired 1 day after surgery, and "stun effects" may linger longer than this (Mestre et al., 2016). However, most past findings suggest changes in both impedance and LFPs occur after electrode implantation, particularly within the first 24 h (Williams et al., 2007; Lempka et al., 2010; Rosa et al., 2010). Furthermore, the logistical constraints and surgical setting of the data acquisition in the current study precluded longer waiting times to acquire the data. Finally, left/right asymmetry of the STN function has been an issue of ongoing investigations with some studies suggesting a lack of such differentiation (Kühn et al., 2005b; Buot and Yelnik, 2012; Lambert et al., 2012). However, future studies with a greater sample size are needed to clarify if stimulation of left asymmetry and recording from right asymmetry and vice-versa has a differential pattern of affecting the emotional behavior and spectral profile of STN signals. STN stimulation and its effects on scalp EEG, especially the high-density EEG are warranted which can delineate the left/right asymmetry effects of STN stimulation.

In conclusion, we show the capacity for acute low-frequency STN stimulation to synchronize physiological activity at the

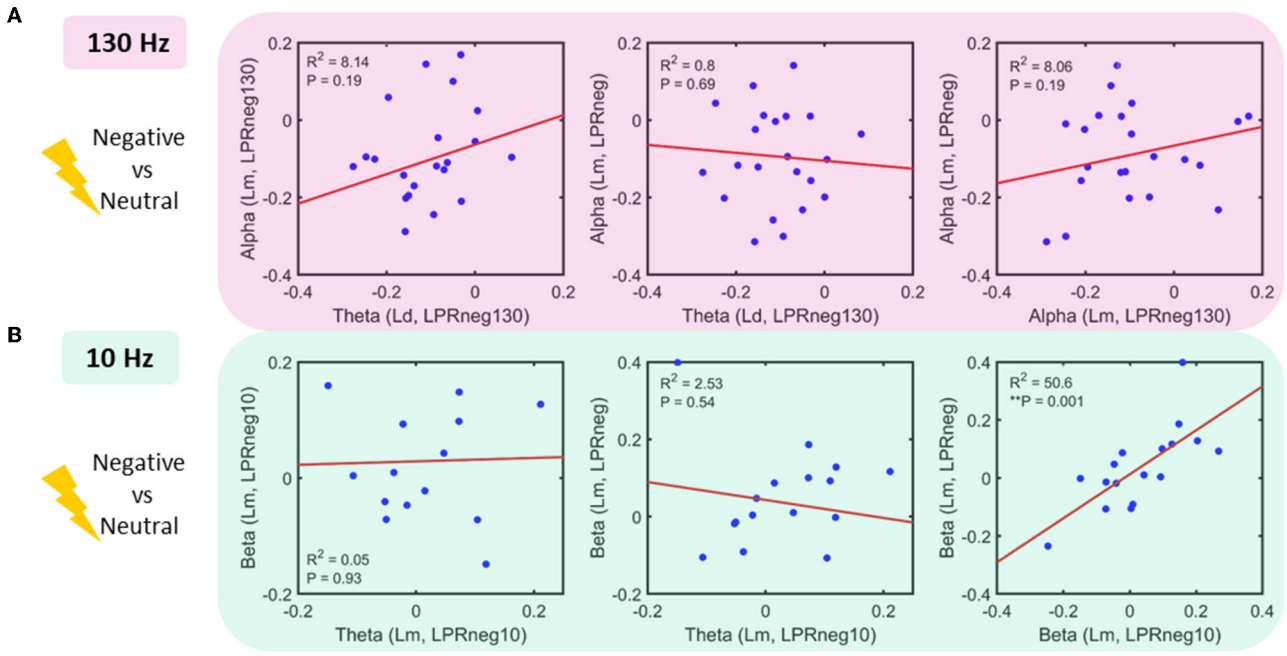

FIGURE 4
Power interactions between frequency bands **(A)** 130 Hz stim task: linear regression fit in pairs of the band as a function of location and power (log of power ratio–LPR, see methods): No significant relationship was found **(B)** 10 Hz stim task: linear regression fit in the pairs of a band as a function of location and power. Beta power for 10 Hz stimulation and unstimulated condition shows a significant positive relationship.

same frequency with evidence for physiological and cognitive generalization effects. Together, this provides evidence for the role of precision neuromodulation approaches and closed-loop deep brain stimulation for the advancement of neurological and neuropsychiatric therapies.

Data availability statement

The data for this project were acquired from patients undergoing clinical care and consenting for additional research protocols. Researchers wishing to access these data will require local ethics approval and a data sharing agreement with Ruijin Hospital, Shanghai, China. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS: formal analysis, investigation, methodology, resources, software, visualization, writing—original draft, review, and editing. NM: data curation, formal analysis, investigation, methodology, resources, software, visualization, and writing—review and editing. AM: conceptualization, data acquisition, data curation, resources, and writing—review and editing. QD: data acquisition, data curation, formal analysis, software, and visualization. LW: data acquisition and data curation. YZ: data acquisition, data curation, funding acquisition, investigation, and project administration. BS: data acquisition, funding acquisition, and project administration. DL: experimental planning and logistics, funding of the experimental study, patient recruitment, surgical evaluation, and data acquisition. VV: conceptualization, funding acquisition, project administration, methodology, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1181635/full#supplementary-material

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Effects of deep brain stimulation on quantitative sleep electroencephalogram during non-rapid eye movement in Parkinson's disease

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Introduction: Sleep dysfunction is frequently experienced by people with Parkinson's disease (PD) and negatively influences quality of life. Although subthalamic nucleus (STN) deep brain stimulation (DBS) can improve sleep in PD, sleep microstructural features such as sleep spindles provide additional insights about healthy sleep. For example, sleep spindles are important for better cognitive performance and for sleep consolidation in healthy adults. We hypothesized that conventional STN DBS settings would yield a greater enhancement in spindle density compared to OFF and low frequency DBS.

Methods: In a previous within-subject, cross-sectional study, we evaluated effects of low (60 Hz) and conventional high (≥130 Hz) frequency STN DBS settings on sleep macroarchitectural features in individuals with PD. In this *post hoc*, exploratory analysis, we conducted polysomnography (PSG)-derived quantitative electroencephalography (qEEG) assessments in a cohort of 15 individuals with PD who had undergone STN DBS treatment a median 13.5 months prior to study participation. Fourteen participants had unilateral DBS and 1 had bilateral DBS. During three nonconsecutive nights of PSG, the participants were assessed under three different DBS conditions: DBS OFF, DBS LOW frequency (60 Hz), and DBS HIGH frequency (≥130 Hz). The primary objective of this study was to investigate the changes in sleep spindle density across the three DBS conditions using repeated-measures analysis of variance. Additionally, we examined various secondary outcomes related to sleep qEEG features. For all participants, PSG-derived EEG data underwent meticulous manual inspection, with the exclusion of any segments affected by movement artifact. Following artifact rejection, sleep qEEG analysis was conducted on frontal and central leads. The measures included slow wave (SW) and spindle density and morphological characteristics, SW-spindle phase-amplitude coupling, and spectral power analysis during non-rapid eye movement (NREM) sleep.

Results: The analysis revealed that spindle density was significantly higher in the DBS HIGH condition compared to the DBS LOW condition. Surprisingly, we found that SW amplitude during NREM was significantly higher in the DBS LOW condition compared to DBS OFF and DBS HIGH conditions. However, no significant differences were observed in the other sleep qEEG features during sleep at different DBS conditions.

Conclusion: This study presents preliminary evidence suggesting that conventional HIGH frequency DBS settings enhance sleep spindle density in PD. Conversely, LOW frequency settings may have beneficial effects on increasing slow wave amplitude during sleep. These findings may inform mechanisms underlying subjective improvements in sleep quality reported in association with DBS. Moreover, this work supports the need for additional research on the influence of surgical interventions on sleep disorders, which are prevalent and debilitating non-motor symptoms in PD.

KEYWORDS

Parkinson's disease, sleep spindles, sleep, cognition, sleep qEEG, Deep brain stimulation

Introduction

Although non-motor Parkinson disease (PD) features have been recognized since the original description of the disease by James Parkinson in 1817, only recently have the prevalence and impact of these non-motor symptoms become the focus of intense study (Parkinson, 2002; Chaudhuri et al., 2006). Sleep disorders are among the most common non-motor manifestations of PD, affecting 64–98% of patients (Lees et al., 1988; Barone et al., 2009). As sleep contributes to the regulation of many physiological homeostatic processes, sleep disturbance has a significant impact on quality of life in PD (Gallagher et al., 2010; Gómez-Esteban et al., 2011; Avidan et al., 2013). Though numerous symptomatic therapies exist, the treatment of sleep disorders in PD is limited by a lack of adequately powered, randomized studies providing high quality evidence (Chahine et al., 2017; Baumgartner et al., 2021).

Deep brain stimulation (DBS) is an established, effective therapy for the treatment of motor symptoms of PD (Deuschl et al., 2006; Schuepbach et al., 2013; Krack et al., 2019), though studies have shown that DBS can also improve non-motor symptoms, including sleep (Arnulf et al., 2000; Iranzo et al., 2002; Monaca et al., 2004). Subthalamic nucleus (STN) DBS has been shown to increase total sleep time, decrease wakefulness after sleep onset, and increase time spent in non-rapid eye movement (NREM) stage 2 (N2) sleep (Arnulf et al., 2000; Monaca et al., 2004). Still, results are mixed, with other studies showing a trend towards a decrease in N2 sleep (though not reaching statistical significance; Iranzo et al., 2002), or no change in N2 sleep but an increase in NREM stage 3 (N3; Monaca et al., 2004).

However, quantification of sleep macroarchitectural features may not fully capture the impact of DBS on sleep. In recent years, technical advancements have allowed for a more detailed quantification of neural oscillations during sleep and advanced the field of sleep research (Weiner and Dang-Vu, 2016). Of particular interest are sleep spindles, which are hallmark oscillations of N2 sleep with a frequency of 9–15 Hz that wax and wane in amplitude, lasting 0.5–3 s (Weiner and Dang-Vu, 2016). They are thought to originate from interactions between thalamic reticular, thalamocortical, and cortical pyramidal networks (Weiner and Dang-Vu, 2016). Sleep spindles have been increasingly recognized as critical for declarative memory, sleep-related memory consolidation, as well as sleep maintenance and continuity (Fernandez and Lüthi, 2020).

In contrast to N2 sleep, pertinent electrophysiological features of N3 sleep include both slow waves (SW, <1 Hz), which occur with lower density in PD patients and may be altered in morphology compared to controls (Memon et al., 2023), and power in the delta frequency range (1.0–4.0 Hz). In prior work, we found a reduced SW density in a group of 56 PD patients compared to controls, but no difference in delta spectral power or SW morphological features including peak-to-peak amplitude and slope (Memon et al., 2023). However, other studies have found conflicting results. For example, Brunner and colleagues found that spectral power in the low delta (0.78–1.2 Hz) range was reduced in a group of 9 *de novo* PD patients compared to controls (Brunner et al., 2002). Finally, in addition to individual NREM EEG oscillations, the temporal relationship between SWs and spindles plays a significant role in neural plasticity. SW and spindle phase-amplitude coupling (PAC) promotes memory consolidation, and declines with physiological aging (Helfrich et al., 2018; Muehlroth et al., 2019). In the only prior study investigating SW-spindle PAC in PD, we found higher non-uniformity in SW-spindle coupling in PD patients compared to controls (Memon et al., 2023).

However, to our knowledge, the impact of DBS on sleep microarchitecture is unexplored. We therefore sought to perform a quantitative EEG (qEEG) analysis of polysomnogram (PSG)-derived data to determine the effect of DBS on sleep spindles (density, amplitude, and peak frequencies), SW (density, amplitude, and slope), SW-spindle PAC (coupling angle, strength, and percentage), and N2/N3 spectral power. This *post hoc* analysis utilizes data collected as part of a previously completed clinical trial investigating the impact of STN DBS on objective sleep outcomes in PD (Amara et al., 2017). This study obtained PSG for 3 non-consecutive nights in PD patients treated with STN DBS: one night with DBS OFF, one with conventional HIGH frequency (≥130 Hz) stimulation, and one with LOW frequency (60 Hz) stimulation, finding no significant difference in sleep macroarchitecture

due to DBS. For the current analysis, we hypothesized that PSG-derived qEEG with DBS at HIGH frequency would show higher spindle density compared to recordings with LOW frequency DBS and DBS OFF.

Methods

Participants

A *post hoc* analysis was conducted on PSG-derived EEG data obtained from a previously completed, within-subject, cross-over study to investigate the impact of STN DBS on objective sleep measures in individuals with PD (Amara et al., 2017). The parent study included 20 individuals with PD who had previously undergone STN DBS treatment (18 unilateral and 2 bilateral STN DBS) at the University of Alabama at Birmingham (UAB) for the management of motor symptoms. At UAB, standard DBS protocol involves the initial placement of a unilateral DBS electrode, with the potential to add a contralateral electrode later if deemed necessary. In all cases, the initial electrode was positioned contralateral to the side of the body most affected by PD. Detailed eligibility criteria have been reported elsewhere (Amara et al., 2017). In summary, eligible participants were those with subjective sleep disturbances, defined as a score > 5 on the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989; Memon et al., 2022) at the time of study entry, and on stable medications and DBS settings, optimized to motor benefit, for at least 6 weeks before enrollment. Exclusion criteria included untreated sleep apnea, narcolepsy, prior brain surgery other than STN DBS, or cognitive impairment that could hinder participation. In the present analysis, additional inclusion criteria required at least 2 of the 3 nights of PSG to have EEG data that was sufficiently free of artifact for the qEEG analysis. Five participants were excluded for not meeting this criterion. Thus, 15 participants were included in the current analysis. Of those 15 participants, 11 participants had PSG for all 3 DBS conditions, 3 participants were missing the ON DBS (≥130 Hz frequency) night, and 1 participant was missing the DBS OFF night, all due to unusable EEG data because of movement or electrical artifacts. The study was registered at clinicaltrials.gov (NCT01769690) and received approval from the UAB Institutional Review Board. All participants gave written informed consent prior to participation.

Assessments

Participants underwent a series of three nonconsecutive nights of PSG. One night involved deactivation of DBS (DBS OFF), another night utilized conventional HIGH-frequency settings (≥130 Hz), and the remaining night employed LOW-frequency settings (60 Hz) using the same amplitude as HIGH frequency condition (Figure 1). Participants adhered to their regular medication regimen throughout the study. The initial PSG study night was with DBS OFF and the order of the HIGH and LOW frequency nights was randomized on the second and third nights, as previously described (Amara et al., 2017). A minimum of three nights separated each PSG session to mitigate any carryover effects. All three PSG studies were completed within a four-week period, and DBS settings were adjusted at 8:00 PM, with the PSG recording beginning at 10 PM. Prior to their initial PSG session, participants were instructed to sleep with DBS OFF for one night at home to ensure their tolerance to sleeping without stimulation. Importantly, no participants withdrew from the study due to intolerance of sleeping with DBS OFF.

Previous research has demonstrated that individuals with monopolar DBS settings experience significant stimulus artifacts during PSG, thereby rendering sleep staging unreliable (Frysinger et al., 2006). Consequently, participants with monopolar configurations ($n = 7$) were systematically reprogrammed to motor-equivalent bipolar settings for the DBS ON and DBS LOW nights, as previously described in detail (Amara et al., 2017). Briefly, bipolar settings were chosen based on participant's initial DBS programming session monopolar survey and equivalent motor efficacy was determined with the Unified Parkinson's Disease Rating Scale (UPDRS) part III (Fahn and Elton, 1987) on the DBS OFF night prior to turning DBS off, and again on the 2nd PSG night to confirm efficacy of chosen settings. The same bipolar settings were used on the 2nd and 3rd study nights with the only difference being frequency (≥130 Hz or 60 Hz). Individual participant DBS settings are shown in Supplemental Table 1.

The PSG recordings included EEG obtained from leads F3, F4, C3, C4, O1, and O2, electrooculogram, electromyography of the mentalis, bilateral anterior tibialis, and bilateral extensor digitorum muscles, thermocouple and nasal pressure for airflow monitoring, respiratory effort with chest and abdominal piezoelectric belts, and pulse oximetry. PSG data were independently scored by two certified sleep technicians and a sleep medicine physician (AWA), who were blinded to the DBS settings.

Quantitative sleep EEG analysis during NREM

Preprocessing

All recorded PSG-derived EEG data were converted into European Data Format (EDF) and imported into MATLAB (version R2021b) for subsequent analysis. To identify potential artifacts, each 30-second epoch was visually inspected. The evaluator responsible for assessing the EEG data (AAM) was blinded to DBS settings (raw trace of one representative participant is shown in Figure 1). Comprehensive visual assessment of the F3 and C3 channels was conducted throughout the entire PSG recording, with the identification and removal of any observed electrical or movement-related artifacts. In cases where continuous artifacts persisted in the F3/C3 leads, the F4/C4 channels were utilized for the analysis.

For the DBS OFF nights, 2.3% of N2 and 0.41% of N3 sleep EEG was rejected due to artifact. For the DBS LOW night, the mean artifact-related data rejection rate was 2.8% for N2 and 0.28% for N3. For the DBS HIGH night, 2.6% of N2 and 1.5% of N3 was eliminated due to artifacts.

Due to the spatial and temporal characteristics of SW and spindles (Fernandez and Lüthi, 2020; Timofeev et al., 2020), SW and delta spectral power were examined within frontal leads. Due to the limited number of participants experiencing N3 sleep, especially during the low frequency night (only 4 participants achieved N3 sleep), we analyzed SW and spectral power data from both N2 and N3 sleep stages combined. Sleep spindles, on the other hand, were assessed within central leads, during N2, the predominant stage during which sleep spindles occur. The coupling between SW and sleep spindles was evaluated across stage N2 and N3 using central channels (Helfrich et al., 2018).

Spectral analysis

The spectral power analysis utilized a Hamming window with a duration of 512 milliseconds and a 50% overlap between consecutive

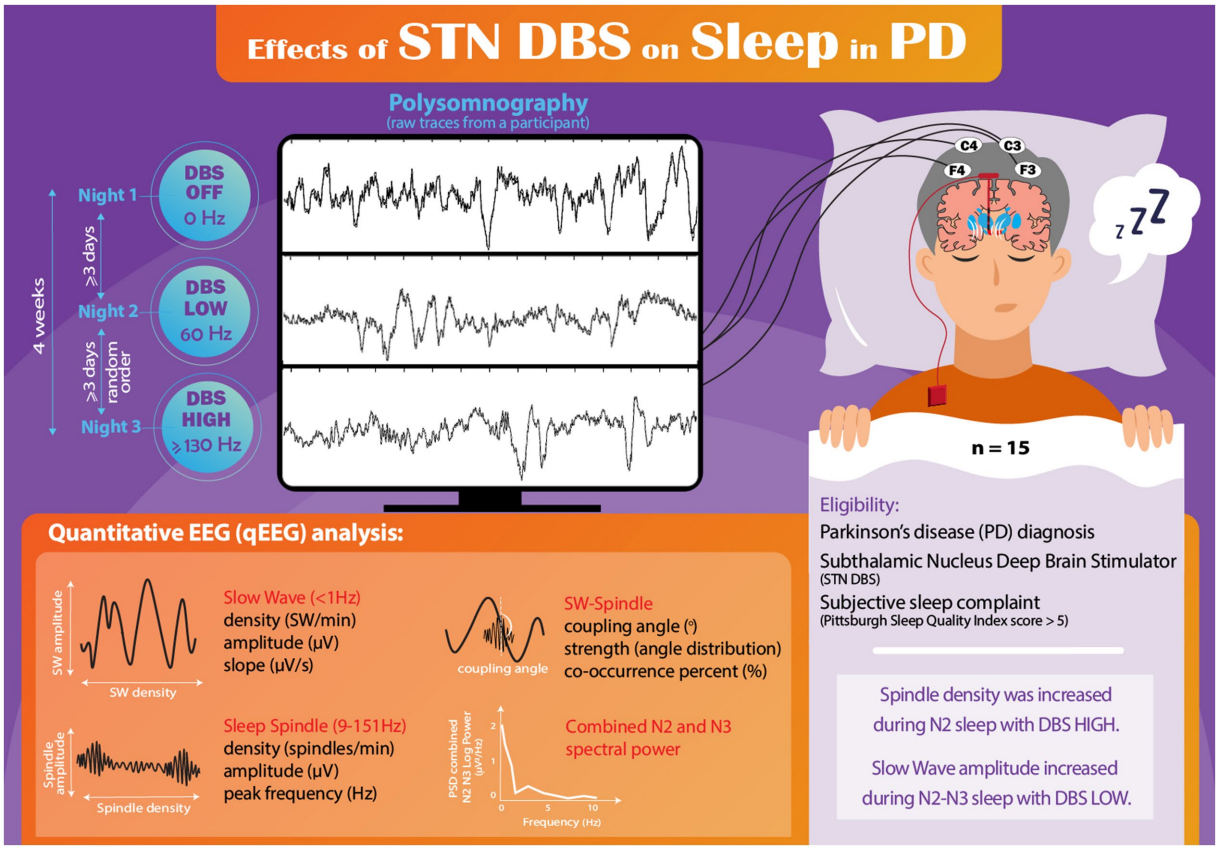

FIGURE 1
Infographic schematic of the study.

windows, resulting in a frequency resolution of 1 Hz. To determine the absolute spectral power within specific frequency ranges, separate averages were computed for stage N2, N3, and combined N2/N3. The frequency ranges of interest included delta (1–4 Hz), theta (5–8 Hz), alpha (9–12 Hz), and beta (13–30 Hz). Supplementary Figure S1 shows the PSD between three different conditions. Note that the DBS LOW-frequency artifact overlaps with electrical line noise at 60 Hz, but that High DBS artifact is visible at 130 Hz.

Scalp-SW and sleep spindle event detection

To detect slow waves (SW) and sleep spindles, EEG data without artifacts were processed using a custom MATLAB script that utilized validated algorithms previously employed in studies involving older adults (Mölle et al., 2011; Staresina et al., 2015; Helfrich et al., 2018; Memon et al., 2023).

For SW detection, zero crossings were identified in the F3 channel, unless artifact in F3 prompted use of F4. SW events were defined based on the following criteria: (1) a frequency filter ranging from 0.16 to 1.25 Hz, (2) duration between 0.8 and 2 s, and (3) peak to peak amplitude threshold determined as the 75th percentile of the amplitude across all stage N2, N3 and combined N2 N3 epochs. Artifact-free individual SW events meeting these criteria were then extracted from the raw EEG signal. The following characteristics were computed and averaged across all stage N2 and N3 epochs from the entire PSG recording due to few participants with N3 ($n = 4$ for LOW DBS night): (1) density (number of events per minute), (2) amplitude (peak-to-peak, measured in microvolts), and (3) slope (measured in volts per millisecond).

For sleep spindle event detection, the following parameters were applied in the C3 channel, unless artifact in C3 prompted use of C4: (1) frequency filter ranging from 9 to 15 Hz, (2) amplitude threshold set at the 75th percentile of the amplitude across all stage N2 epochs, and (3) duration range of 0.5 to 3 s. By utilizing Hilbert's transformation, the analytical amplitude was calculated, and events meeting the specified parameters were automatically extracted. The subsequent sleep spindle characteristics were computed and averaged over all stage N2 epochs from the entire PSG recording: (1) density (number of events per minute), (2) amplitude (peak-to-peak, measured in microvolts), and (3) peak frequency (cycles per second, measured in Hz) for spindles (9–15 Hz), slow spindles (9–11 Hz), and fast spindles (12–15 Hz). The division into slow and fast frequency bins was based on our previous findings that demonstrated a higher slow spindle peak frequency in PD patients compared to non-PD controls (Memon et al., 2023).

SW locked sleep spindle phase-amplitude coupling

Upon identifying individual SW events, the subsequent step involved determining the instantaneous phase angle of these events by applying the Hilbert transformation to the raw signal. Subsequently, the raw signal was subjected to filtering within the frequency range of

9–15 Hz, corresponding to the spindle frequency range. The Hilbert transformation was employed once again on the filtered signal to obtain the instantaneous amplitude. The maximum amplitude of the spindle and its corresponding phase angle of the SW were then identified (Dvorak and Fenton, 2014; Staresina et al., 2015).

The following characteristics were computed for the combined N2 and N3 sleep stages:

(1) Mean SW phase angle in degrees, which was calculated utilizing the CircStat toolbox (Berens, 2009). This measure provides information regarding the average phase angle of the SW events. (2) Coupling angle distribution nonuniformity or strength, which was assessed using the Rayleigh test statistic. This analysis aids in determining the extent of nonuniformity or clustering in the coupling angles between the phase of SW and the amplitude of the spindle.

SW-spindle co-occurrence percent:

Using the aforementioned parameters, SW and sleep spindle events were identified as distinct entities. The subsequent step involved quantifying the SW-spindle co-occurrence percentage, which measures the proportion of SW events that coincide with the occurrence of sleep spindles.

To compute the SW-spindle co-occurrence percentage, each SW event was scrutinized to determine if a detected sleep spindle's center fell within the duration of the SW event. If a sleep spindle was found to co-occur with a specific SW event, it was considered an instance of SW-spindle co-occurrence. The SW-spindle co-occurrence percentage was then calculated by normalizing the number of SW events with co-occurring sleep spindles over the total number of SW events.

Statistical analysis

This study utilized a within-subject, cross-over design to investigate the difference in sleep qEEG morphological features. Statistical analysis was performed using JMP Pro 16 (SAS Institute, Inc., Cary, NC). For the descriptive statistics, the normality of all variables was assessed using the Shapiro–Wilk test. Differences in qEEG morphological characteristics across the different DBS settings were compared with mixed-model repeated-measures analysis of variance. If significant differences were found between the DBS settings, Tukey's honesty significant difference (HSD) multiple comparison procedure was performed to determine which settings were different. Given the exploratory nature of our study, we did not apply a correction for multiple comparisons. Instead, we chose to accept the possibility of Type 1 error to avoid rejecting potential associations that could be missed due to Type II errors resulting from correction procedures.

Results

Participants characteristics

The demographic characteristics of the participants are provided in Table 1. Table 2 displays the sleep characteristics during the OFF, LOW, and HIGH DBS nights. No significant differences were observed between the DBS settings in terms of objective sleep outcomes for these 15 participants, consistent with the previous report of the full cohort of 20 participants (Amara et al., 2017).

TABLE 1 Baseline demographic and clinical characteristics.

Characteristics	Descriptive Statistics (*n*=)
N	15
Age (years)	
Mean ± SD	61.8 ± 9.5
Range	45–77
Sex: *N* (%)	
Male	11 (73.3%)
Female	4 (26.7%)
Duration of disease (DOD; years)	
Mean ± SD	10.0 ± 3.7
Range	5–20
Months since DBS placement	
Median (IQR)	13.5 (8.1–23.4)
Levodopa equivalent dose (LED; mg)	
Mean ± SD	968.9 ± 673.3
Range	0–2247.5
MDS-UPDRS*	
OFF DBS, On medication	
Median (IQR)	31.0 (28.8–40.3)
Side of surgery *N* (%)	
Bilateral	1 (6.7%)
Left	9 (60.0%)
Right	5 (33.3%)

Mean ± SD presented for normally distributed data. Median (IQR) reported for non-normally distributed data.*Performed in the morning following PSG with DBS OFF, medication on.

Quantitative NREM sleep EEG analysis

Sleep spindle characteristics during N2

Sleep spindle density exhibited significant difference between the nights ($F=5.10$, $p=0.014$; Figure 2A; Table 3). Tukey's HSD multiple comparison procedure showed that sleep spindle density was significantly higher on the DBS HIGH night (frequency ≥ 130 Hz) compared to the DBS LOW night. However, no significant differences were observed between the three nights in terms of other spindle morphological features, including peak-to-peak amplitude and peak frequency (Table 3).

Scalp-SW and spectral power analysis and SW morphology during N2 and N3

To assess the dynamics of sleep EEG activity during stage N2 and N3 under various DBS settings, we investigated the spectral power characteristics. There were no observed differences in the power in any of the measured spectral frequency bands (delta, theta, alpha, or gamma) during N2 and N3 sleep across the three DBS settings. However, SW amplitude was significantly different between the three

TABLE 2 Baseline objective sleep characteristics.

Sleep variables	DBS OFF	DBS LOW frequency (60 Hz)	DBS HIGH frequency (≥130 Hz)	*p* value
Sleep efficiency (%)	83 (76–87)	84 (72–89)	86 (73–91)	$F = 0.46$ $p = 0.635$
Total sleep time (min)	381.0 (308.0–400.0)	380.1 (291.0–434.2)	402.5 (342.5–441.6)	$F = 0.92$ $p = 0.412$
Wake after sleep onset (WASO; min)	73.5 (50.1–113.5)	61.6 (39.2–98.5)	44.5 (42.2–89.6)	$F = 0.66$ $p = 0.525$
Sleep latency (min)	8.3 (2.9–14.0)	11.0 (5.5–34.1)	5.5 (3.9–14.0)	$F = 1.58$ $p = 0.223$
N1%	12.0 (7.0–16.0)	13.0 (8.0–21.0)	8.0 (6.0–14.0)	$F = 1.26$ $p = 0.299$
N1 time (min)	46 (26–53.5)	41.5 (23.0–60.5)	30.0 (20.0–42.2)	$F = 0.25$ $p = 0.784$
N2%	71.7 ± 13.1	66.1 ± 20.4	72.2 ± 12.4	$F = 1.34$ $p = 0.279$
N2 time (min)	248.6 ± 66.7	249.5 ± 106.0	274.1 ± 103.1	$F = 1.07$ $p = 0.356$
N3% Range	1.0 (0.0–9.0) 0.0–15.0	0.0 (0.0–0.0) 0.0–19.0	0.0 (0.0–3.0) 0.0–11.0	$F = 1.77$ $p = 0.189$
N3 time (min) Range	3.5 (0.0–37.0) 0.0–60.0	0 (0.0–1.0) 0.0–73.0	0.5 (0.0–311.5) 0.0–28.0	$F = 2.58$ $p = 0.094$
REM %	11.5 ± 9.7	13.9 ± 8.9	12.7 ± 8.5	$F = 0.74$ $p = 0.487$
REM time (min)	42.8 ± 34.4	51.7 ± 35.0	45.2 ± 31.0	$F = 0.69$ $p = 0.510$
Apnea hypopnea index (events per hour)	0.4 (0.0–3.5)	0.3 (0.0–2.2)	0.5 (0.0–2.8)	$F = 0.59$ $p = 0.563$

Mean ± SD presented for normally distributed data. Median (IQR) reported for non-normally distributed data. N1: non-REM stage1; N2: Non-REM stage 2; N3: non-REM stage 3; REM: rapid eye movement sleep.

nights, with Tukey's HSD procedure showing that SW amplitude was higher on the DBS LOW night compared to DBS OFF and HIGH (Figure 2B; Table 3). There were no statistically significant differences found between the nights in terms of SW morphological characteristics, including density and slope (Table 3).

SW-spindle phase amplitude coupling characteristics during N2 and N3

There were no significant differences in average phase angle of spindle-SW coupling, the nonuniformity of coupling angles, or the co-occurrence percentage of spindle-SW coupling between PSG nights on different DBS settings (Table 3).

Discussion

In this *post hoc* analysis of PSG-derived EEG data from a within-subject, crossover study of the effects of HIGH and LOW frequency DBS on objective sleep outcomes, sleep spindle density was higher with DBS on at HIGH frequency than with DBS at LOW frequency. In addition, slow wave amplitude during N2 and N3 sleep was higher with DBS at LOW frequency than with DBS OFF or at HIGH frequency. We did not detect differences between the three conditions in spindle amplitude or peak frequency, SW density or slope, SW-spindle PAC, or spectral power across canonical frequency bands during N2/N3 sleep. Although exploratory, these data may inform future studies investigating stimulation-induced changes in sleep microarchitecture and therefore provide a potential mechanism for intervening on sleep dysfunction in PD with DBS.

STN DBS, although not directly targeted or programmed to address sleep, has been shown to improve both subjective and objective sleep outcomes in PD. Multiple studies have demonstrated improvements in self-reported sleep quality and sleepiness, as measured by the Parkinson's Disease Sleep Scale (PDSS, PDSS-2; Hjort et al., 2004; Chahine et al., 2011; Nishida et al., 2011; Breen et al., 2015; Deli et al., 2015), PSQI (Iranzo et al., 2002; Monaca et al., 2004; Amara et al., 2012), and Epworth Sleepiness Scale (ESS; Chahine et al., 2011; Baumann-Vogel et al., 2017). In the largest PSG-based study of the effects of DBS on sleep, STN DBS improved total sleep time and sleep efficiency, associated with increased N3 sleep (42.6 ± 34.9 min before DBS, 53.8 ± 43.3 min after DBS) in 50 PD participants (Baumann-Vogel et al., 2017). In another study, total sleep time increased with

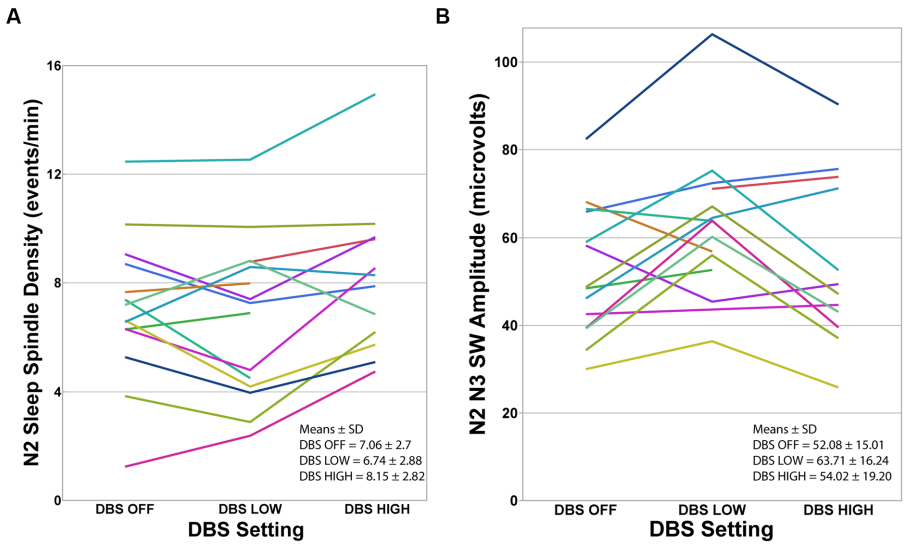

FIGURE 2
Individual participants at each DBS setting. **(A)** Sleep spindle density during N2 was significantly different between the three DBS conditions using mixed-model repeated-measures analysis of variance ($F = 5.10$, $p = 0.014$). Tukey's HSD procedure showed that spindle density was higher during DBS HIGH-frequency compared to DBS LOW-frequency. **(B)** Slow Wave amplitude was significantly different between the three DBS conditions using mixed-model repeated-measures analysis of variance ($F = 5.78$, $p = 0.009$). Tukey's HSD procedure showed that SW amplitude was higher during N2 and N3 in DBS LOW-frequency night compared to DBS HIGH-frequency and DBS OFF. Note that data from one participant during the OFF-night assessment and three participants during the HIGH-night assessment were excluded because EEG was unusable due to movement artifacts.

stimulation on compared to off in 10 PD participants, primarily driven by an increase in N2 sleep (180 ± 23 min with DBS on, 125 ± 16 min with DBS off; Arnulf et al., 2000). Another study of 10 PD patients found that total sleep time increased with DBS on compared to off, but this was due to increases in N3 (69.6 ± 35.4 min with DBS on, 27.7 ± 26.9 min with DBS off) and REM (68.8 ± 35 min with DBS on, 43.1 ± 22.7 min with DBS off; Monaca et al., 2004). There was no significant difference in the time spent in N2 sleep. In the parent study upon which the present analysis is based, there was no difference in total sleep time, sleep efficiency, wakefulness after sleep onset, or time spent in stages N1, N2, N3, or REM between nights with DBS OFF, LOW frequency, or HIGH frequency DBS (Amara et al., 2017). This difference may be related to predominantly unilateral DBS in the current study, compared to bilateral DBS in most other studies. Another possible explanation for this heterogeneity amongst studies is the limitation of qualitative sleep staging. According to the American Academy of Sleep Medicine guidelines, N2 sleep is scored only if K-complexes or sleep spindles are observed during a 30-s epoch (Berry et al., 2018). However, sleep spindles in PD patients are of lower density and have several other morphological differences (including longer duration, slower frequency, and higher maximum peak-to-peak amplitudes) compared to age-matched controls (Christensen et al., 2015; Latreille et al., 2015). This variability in appearance could possibly affect the threshold for spindle detection, and therefore alter the qualitative sleep stage determination.

Nonetheless, DBS does seem to reliably improve at least subjective sleep quality and, in some studies, objective sleep outcomes. Our study provides the first evidence that increased sleep spindle density with high-frequency DBS could be one potential mechanism through which DBS can improve sleep. Spindles play a crucial role in maintaining and sustaining sleep (Astori et al., 2013; Weiner and Dang-Vu, 2016), and as such, their promotion by means of high frequency STN stimulation may underly the improvements in N2 and N3 sleep as well as subjective sleep quality found in the aforementioned studies.

In the only prior study to examine the effect of DBS on sleep spindles, Arnulf et al. recorded sleep spindle density in 6 patients (4 PD, 2 Essential Tremor) during treatment with stimulation of the ventral intermediate nucleus of the thalamus (VIM) and off stimulation (Arnulf et al., 2000). They found no difference in spindle density on versus off stimulation, suggesting that VIM stimulation was not directly affecting spindle generation. The contrasting results of this study with ours may be due to methodological differences, including their inclusion of patients with Essential Tremor. Alternatively, it is possible that these results imply a differential effect of STN versus VIM stimulation on sleep spindles. Although a definite pathophysiological mechanism remains elusive, a growing body of evidence implicates the basal ganglia as an important node in a brain-wide network critical for the maintenance of sleep (Liu and Dan, 2019). In healthy primates, basal ganglia neurons have been shown to exhibit slow oscillations in firing similar to those observed in cortical neurons (Mizrahi-Kliger et al., 2018). Recording of local field potentials (LFPs) in the basal ganglia demonstrate dramatically reduced slow oscillations compared with thalamocortical networks (Mizrahi-Kliger et al., 2018). In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of parkinsonism, increased power in the alpha and low beta range (10–17 Hz) during NREM was seen in GPe, GPi, and STN (Mizrahi-Kliger et al., 2020). This increase was associated with a decrease in the power of slow oscillatory firing of the basal ganglia, and a decreased propensity for sleep and an increased frequency of awakenings. Furthermore, beta oscillations became more prominent in the approach to awakenings, and in humans, STN LFPs show that beta activity is reduced during NREM (Thompson et al., 2018; van Rheede et al., 2022). Modulation of pathologic synchronized oscillatory activity by high frequency

TABLE 3 Sleep quantitative electroencephalographic outcomes for each DBS settings.

Sleep qEEG variables	DBS OFF*	DBS LOW frequency (60 Hz)*	DBS HIGH frequency (≥130 Hz)**	*p* value
N2 spindle density	7.06 ± 2.70	6.74 ± 2.88	8.15 ± 2.82	F = **5.10** p = **0.014**
N2 spindle amplitude	11.82 (10.37–12.90)	12.11 (10.45–14.00)	12.11 (10.31–13.17)	F = 0.19 p = 0.825
N2 spindle peak-frequency	11.20 ± 0.57	11.16 ± 0.61	11.33 ± 0.55	F = 1.43 p = 0.260
N2 spindle peak slow frequency	10.25 ± 0.18	10.24 ± 0.22	10.29 ± 0.13	F = 0.57 p = 0.576
N2 spindle peak fast frequency	13.18 ± 0.09	13.19 ± 0.12	13.24 ± 0.12	F = 1.23 p = 0.311
N3 slow wave density	11.48 ± 4.25	12.91 ± 3.01	10.11 ± 3.44	F = 1.91 p = 0.193
N2 N3 slow wave density	3.83 ± 1.07	3.27 ± 1.20	3.53 ± 1.22	F = 1.22 p = 0.312
N3 slow wave amplitude	52.25 ± 15.00	74.73 ± 2.10	59.80 ± 21.14	F = 1.69 p = 0.227
N2 N3 slow wave amplitude	52.08 ± 15.06	63.71 ± 16.24	54.20 ± 19.20	***F* = 5.78** ***p* = 0.009**
N3 slow wave slope	91.33 ± 27.25	125.97 ± 17.40	101.50 ± 39.71	F = 3.02 p = 0.093
N2 N3 slow wave slope	78.20 (63.33–101.13)	98.93 (86.57–127.49)	82.46 (64.50–204.16)	F = 1.58 p = 0.225
N2 N3 SW-spindle phase amplitude coupling angle	−2.98 ± 1.17	−1.80 ± 1.29	0.52 ± 1.31	F = 1.34 p = 0.27
N2 N3 SW-spindle coupling strength	131.88 (41.04–290.13)	143.29 (87.55–381.44)	92.78 (57.81–294.74)	F = 1.02 p = 0.376
N2 N3 SW-spindle coupling percent	1.39 ± 0.70	1.35 ± 0.91	1.57 ± 1.02	F = 0.72 p = 0.497
N3 delta power 1–4 Hz	114.08 ± 44.51	170.86 ± 33.71	124.48 ± 66.10	F = 1.26 p = 0.320
N2 N3 delta power 1–4 Hz	56.89 (35.50–67.84)	65.87 (44.18–70.57)	55.03 (50.11–110.97)	F = 1.44 p = 0.255
N3 theta 4–8 Hz	10.73 (7.0–11.70)	11.55 (10.36–21.46)	9.11 (6.26–13.83)	F = 2.74 p = 0.104
N2 N3 theta 4–8	8.25 (5.55–9.77)	8.11 (6.12–10.53)	7.96 (5.84–11.02)	F = 1.84 p = 0.180
N3 alpha 9–12	1.99 ± 4.51	2.28 ± 4.49	3.90 ± 2.13	F = 0.395 p = 0.684
N2 N3 alpha 9–12	3.45 (2.66–5.10)	3.32 (2.89–6.43)	3.54 (2.38–4.51)	F = 0.454 p = 0.640
N3 beta 12–30	0.54 ± 0.24	0.63 ± 0.15	0.52 ± 0.22	F = 3.93 p = 0.055
N2 N3 beta 12–30	0.68 ± 0.22	0.72 ± 0.26	0.73 ± 0.26	F = 1.67 p = 0.209

*N = 14.
**N = 12.
Bold values are statistically significant.

DBS may therefore promote the return of physiological sleep structure, including spindle formation, and thus allow for the maintenance of sleep.

The other significant finding of this study was a difference in SW amplitude in combined N2 and N3 sleep between the three stimulation conditions. Interestingly, SW amplitude was highest with

LOW frequency DBS, and lower in HIGH frequency DBS and OFF DBS. The significance of this result is uncertain and must be interpreted with caution. It is important to note that when only N3 sleep was examined, there was no difference in SW amplitude between the three conditions. This may be due to the low number of participants achieving N3 sleep in the DBS low frequency condition (only four subjects). Another possibility is that due to the automated nature of the analysis, K-complexes in N2 sleep may have been interpreted as slow waves and thus caused the discrepancy between N2 and combined N2 and N3 sleep. Still, this finding could motivate future studies of low frequency DBS, perhaps lower than 60 Hz, on SW activity.

Strengths of this study include the utilization of PSG-derived EEG data from a within-subject, crossover study and the use of qEEG analytical methods. An important limitation is the *post hoc* and exploratory nature of the analysis, which is prone to biased interpretation. Nonetheless, such retrospective analyses can provide valuable insights and generate new hypotheses for further exploration and investigation. This study is also limited by the absence of N3 sleep for several participants during the night of low frequency DBS, preventing analysis of N3 sleep for all but four subjects. The exclusion of artifact-contaminated PSG data also may limit our accuracy, though as above the amount of data rejected due to artifact was generally low (2.3–2.8% N2, 0.28–1.5% N3). Furthermore, this was addressed in the parent clinical trial by employing bipolar stimulation configurations in all subjects, which may be less likely to cause stimulation artifact (Frysinger et al., 2006; Amara et al., 2017).

In conclusion, this is the first study to examine the effects of STN DBS on sleep spindle density as well as several other qEEG outcomes during NREM in PD patients. DBS likely has a beneficial therapeutic effect on sleep in PD, which may be due in part to increased sleep spindle density during N2 sleep. Given the exploratory nature of this study, it will be critical for future studies to further examine the potential therapeutic effect of DBS on sleep microarchitecture. These findings have important therapeutic implications and represent a potentially substantial advancement in the search for improved treatments for sleep dysfunction in PD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Alabama at Birmingham IRB. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AM: Conceptualization, Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review and editing, Data curation. BE: Data curation, Formal Analysis, Methodology, Writing – review and editing. AB: Writing – original draft, Writing – review and editing. AG: Data curation, Formal Analysis, Methodology, Writing – review and editing. CC: Data curation, Visualization, Writing – review and editing. ZI: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – review and editing. AJ: Data curation, Methodology, Writing – review and editing. SM: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – review and editing. AA: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Supervision, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1269864/full#supplementary-material

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Medication only improves limb movements while deep brain stimulation improves eye and limb movements during visually-guided reaching in Parkinson's disease

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Background: Antiparkinson medication and subthalamic nucleus deep brain stimulation (STN-DBS), two common treatments of Parkinson's disease (PD), effectively improve skeletomotor movements. However, evidence suggests that these treatments may have differential effects on eye and limb movements, although both movement types are controlled through the parallel basal ganglia loops.

Objective: Using a task that requires both eye and upper limb movements, we aimed to determine the effects of medication and STN-DBS on eye and upper limb movement performance.

Methods: Participants performed a visually-guided reaching task. We collected eye and upper limb movement data from participants with PD who were tested both OFF and ON medication (n = 34) or both OFF and ON bilateral STN-DBS while OFF medication (n = 11). We also collected data from older adult healthy controls (n = 14).

Results: We found that medication increased saccade latency, while having no effect on reach reaction time (RT). Medication significantly decreased saccade peak velocity, while increasing reach peak velocity. We also found that bilateral STN-DBS significantly decreased saccade latency while having no effect on reach RT, and increased saccade and reach peak velocity. Finally, we found that there was a positive relationship between saccade latency and reach RT, which was unaffected by either treatment.

Conclusion: These findings show that medication worsens saccade performance and benefits reaching performance, while STN-DBS benefits both saccade and reaching performance. We explore what the differential beneficial and detrimental effects on eye and limb movements suggest about the potential physiological changes occurring due to treatment.

KEYWORDS

Parkinson's disease, antiparkinson medication, levodopa, subthalamic nucleus deep brain stimulation, saccade, reaching

1. Introduction

Two common treatments for Parkinson's disease (PD) are antiparkinson medication and subthalamic nucleus deep brain stimulation (STN-DBS). While both treatments effectively improve the motor signs of PD, the mechanisms by which treatment improves behavior may be different. An indirect way to assess these mechanisms is to determine the treatment effects on different effectors, such as the eyes and upper limbs. This will help elucidate how treatments are affecting multiple neural circuits. However, treatment effects on eye and upper limb performance have typically been assessed in separate experiments with different tasks. We aimed to assess and better understand how the different treatments of PD affect both eye and upper limb movements during the same movement task using comparable outcomes. We focused on two aspects of eye and upper limb movement: latency/reaction time (RT) and peak velocity.

The results from separate eye only and upper limb only movement tasks suggest that antiparkinson medication may have differential effects on the eyes and upper limbs. We have recently shown that medication increased saccade latency (Munoz et al., 2022), confirming the findings of previous studies (Müller et al., 1994; Michell et al., 2006; Hood et al., 2007; Dec-Ćwiek et al., 2017; Lu et al., 2019; Waldthaler et al., 2019). However, other studies have reported that medication does not have a significant effect on saccade latency (Gibson et al., 1987; Rascol et al., 1989; Temel et al., 2009; van Stockum et al., 2012; Cubizolle et al., 2014; Bakhtiari et al., 2020), which could be due to suboptimal medication doses (Munoz et al., 2022). Conversely, the medication effect on simple RT tasks evaluating upper limb movement has typically lacked statistical significance, however, there has been a consistent pattern of medication decreasing simple RT within all (Velasco and Velasco, 1973; Bloxham et al., 1987; Pullman et al., 1988, 1990; Starkstein et al., 1989; Jahanshahi et al., 1992; Fern-Pollak et al., 2004; Ingram et al., 2021) but one study (Müller and Harati, 2020). Additionally, one study found this decrease in latency with medication to be statistically significant (Montgomery and Nuessen, 1990). Overall, these findings suggest that medication significantly increases saccade latency and decreases upper limb simple RT, but not significantly.

During the visually-guided saccade task, medication typically decreased saccade peak velocity, either significantly (Munoz et al., 2022) or not significantly (Dec-Ćwiek et al., 2017; Lu et al., 2019). Conversely, studies reported that medication typically increased the peak velocity of simple upper limb movements during reach-to-grasp tasks (Castiello et al., 2000; Negrotti et al., 2005; Schettino et al., 2006), arm abduction to match a target (Baroni et al., 1984), wrist flexion (Berardelli et al., 1986; Johnson et al., 1994), elbow flexion (Robichaud et al., 2002; Vaillancourt et al., 2004), and reach- or point-to-target tasks (Kelly et al., 2002; Camarda et al., 2005). Similarly, medication has improved finger tapping speed and pronation-supination speed (Brzezicki et al., 2023). Taken together, previous literature suggests that medication will decrease saccade peak velocity but increase upper limb peak velocity. However, the effects of medication on both eye and limb movements have not been tested using a single task and cohort of participants with PD.

Unlike studies examining the effects of medication, the previous literature evaluating the effects of STN-DBS suggest that bilateral STN-DBS may have similar effects on eye and upper limb movements. Using the visually-guided saccade task, most studies have shown that STN-DBS decreased saccade latency compared to OFF stimulation, typically significantly (Fawcett et al., 2007, 2010; Sauleau et al., 2008; Temel et al., 2008, 2009; Yugeta et al., 2010; Antoniades et al., 2012a,b, 2015; Dec-Ćwiek et al., 2017; Goelz et al., 2017; Bakhtiari et al., 2020), but occasionally not significantly (Rivaud-Péchoux et al., 2000; Lohnes and Earhart, 2012; Pinkhardt et al., 2012; Nilsson et al., 2013). Similarly to saccade latency, studies found that bilateral STN-DBS decreased upper limb RT during a simple RT task, either significantly (Brown et al., 1999; Temel et al., 2006; Antoniades et al., 2012b) or trending toward significance (Kumru et al., 2004). Additionally, one study compared the effect of STN-DBS on visually-guided saccade latency and button press RT. They found that STN-DBS decreased both latency and RT (Antoniades et al., 2012b), but other aspects of movement, such as peak velocity, were not evaluated. Overall, these findings suggest that bilateral STN-DBS will decrease both saccade latency and reach RT.

Previous studies using the visually-guided saccade task reported that bilateral STN-DBS increased saccade peak velocity, either significantly (Nilsson et al., 2013) or not significantly (Pinkhardt et al., 2012; Dec-Ćwiek et al., 2017). Similarly, STN-DBS has repeatedly been found to increase peak velocity of upper limb movements, such as reach-to-grasp (Dafotakis et al., 2008), finger tapping (Dafotakis et al., 2008; Tamás et al., 2016), repetitive pointing (Dafotakis et al., 2008), hand grasping (Tamás et al., 2016), elbow flexion (Vaillancourt et al., 2004), pronation/supination (Tamás et al., 2016), and cued upper limb joint movements (Joundi et al., 2012). This would be expected as STN-DBS is a common treatment of PD because it has been proven to improve motor

function (Limousin et al., 1995; Pollak et al., 1996; Krack et al., 1998; Brown et al., 1999; Thobois et al., 2002; Rodriguez-Oroz et al., 2005). Taken together, previous literature suggests that STN-DBS will increase saccade and upper limb peak velocity. However, the effects of STN-DBS on eye and upper limb movements have mostly been evaluated separately, limiting direct comparisons.

This study investigated the effects of antiparkinson medication and bilateral STN-DBS on the oculomotor and skeletomotor systems during a task requiring both eye and upper limb movement. First, we determined the effect of medication on saccade and reach latency/RT and peak velocity. We hypothesized that medication would increase saccade latency while having no effect on or decreasing reach RT and would decrease saccade peak velocity while increasing reach peak velocity. Second, we determined the effect of bilateral STN-DBS on saccade and reach latency/RT and peak velocity. We hypothesized that STN-DBS would decrease both saccade latency and reach RT and would increase both saccade and reach peak velocity. Third, we determined the relationship between saccade latency and reach RT for a cohort of people with PD tested OFF and ON medication, a cohort of people with PD tested OFF and ON STN-DBS, and healthy controls to evaluate whether treatment has an impact on this relationship.

2. Materials and methods

2.1. Participants

Northwestern University and Rush University Medical Center Institutional Review Boards approved this study, and all experiments were completed in accord with the Helsinki Declaration of 1975. We obtained informed consent from all participants. Participants with PD were recruited from the movement disorder clinics at both institutions. Participants with PD were examined by a movement disorders neurologist and met the United Kingdom PD Society brain bank clinical diagnostic criteria (Hughes et al., 1992a,b; Berardelli et al., 2013) but had no neurological comorbidities, while healthy controls had no reported history of any neurological disorders. All participants had (1) normal or corrected-to-normal visual acuity, (2) no eye movement abnormalities, such as blepharospasm, double vision, and/or eyelid opening apraxia, and (3) the ability to understand and perform the experimental task during intake. All participants were right-hand dominant, as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971).

To examine the medication effect, 34 individuals with PD (28 males, 6 females) who were treated with antiparkinson medication completed testing of the visually-guided reaching task (**Table 1**). To examine the STN-DBS effect, we recruited 14 individuals with PD who had high-frequency bilateral STN-DBS. Three participants were unable to complete testing OFF STN-DBS. Therefore, the STN-DBS effect analysis included 11 individuals with PD (11 males) who were treated with bilateral STN-DBS (**Table 1**). Individuals were tested 8 months post-surgery on average (range: 6–12 months). Finally, we also tested 17 older adult healthy controls, but 3 were excluded due to a high Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III motor score (>12), a low Montreal Cognitive Assessment (MoCA) score (<18), or fatigue preventing the participant from successfully completing the task. The final healthy control group included 14 participants (12 males, 2 females) (**Table 1**).

2.2. Experimental conditions

To determine the medication effect, data collection took place over 3 days: 1 day for intake and 2 days for testing. During intake, participants with PD were consented, were administered the MoCA, and practiced the experimental tasks while ON medication. Testing occurred over the next 2 days: 1 day OFF medication and 1 day ON medication, with the order of medication condition randomized across participants. For OFF medication testing, participants withdrew from all antiparkinson medications for at least 12-h before the start of testing (Langston et al., 1992). For ON medication testing, participants took their medications as usual. To verify that participants were in the "off state" or "on state," the experimenter confirmed with the participant that they felt "off" or "on" before testing began. MDS-UPDRS Part III was administered right before testing each day.

To determine the bilateral STN-DBS effect, data collection took place over 5 days: 1 day for intake and 4 days for testing. Intake was completed ON medication and ON bilateral STN-DBS and otherwise was identical to the intake day of the medication effect participants. Testing occurred over the next 4 days: 1 day OFF STN-DBS, 1 day with only the left stimulator on, 1 day with only the right stimulator on, and 1 day ON bilateral stimulation with the order of STN-DBS condition randomized across subjects. Only data from the OFF STN-DBS and ON bilateral STN-DBS conditions are presented in this manuscript. Stimulators were turned OFF at least 3-h prior to testing (Temperli et al., 2003). ON bilateral

TABLE 1 Characteristics of participants with Parkinson's disease in the medication and STN-DBS effect analyses and healthy controls.

	Medication effect (n = 34)	STN-DBS effect (n = 11)	Healthy controls (n = 14)
Sex (M/F)	28/6	11/0	12/2
Age (years)	65.88 ± 3.86	66.64 ± 3.17	65.43 ± 4.24
Disease duration (years)	7.12 ± 4.30	10.27 ± 4.84	.
Time since surgery (months)	.	8.27 ± 1.74	.
MoCA	27.68 ± 1.92	27.00 ± 2.00	27.21 ± 1.63
MDS-UPDRS Part III			
Off meds	43.24 ± 15.06	.	2.93 ± 2.30
On meds	32.03 ± 11.55	.	.
Off meds, Off DBS	.	50.55 ± 14.27	.
Off meds, On DBS	.	19.55 ± 8.17	.
Levodopa equivalent daily dose (mg)	790.00 ± 658.46	405.45 ± 288.92	.

Values are mean ± standard deviation. DBS, deep brain stimulation; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; mg, milligrams; MoCA, Montreal Cognitive Assessment.

stimulation testing was completed on clinical stimulation settings (**Table 2**). All testing was completed OFF medication after at least 12-h overnight withdrawal (Langston et al., 1992). MDS-UPDRS Part III was administered right before testing each day.

For healthy controls, intake and testing were completed in 1 day. Testing for all participants included a series of 6 different eye and upper limb movement tasks, but only data from one, the visually-guided reaching task, is reported in this manuscript.

2.3. Instrumentation

Participants sat upright in a height-adjustable chair with their chin placed on a chin rest to minimize head movement. We recorded binocular eye movements at 500 Hz using an infrared camera-based eye-tracking system (Eyelink II, SR Research Ltd, Ottawa, ON, Canada). We recorded head, upper limb, and robotic arm movements at 240 Hz using a three-dimensional motion capture system (Optotrak 3020, Northern Digital, Waterloo, ON, Canada). To capture head and upper limb movements, participants had infrared light-emitting diodes (iLED) attached to the eye tracking system on the head and another iLED attached to their right index finger adjacent to their fingernail. To capture the robotic arm movements, another iLED was attached to the end of the robotic arm. Eye, head, upper limb, and robotic arm movements were synchronized, after down-sampling the eye-tracking data to 240 Hz, and stored using The MotionMonitor (Innovative Sports Training, Chicago, IL, USA).

The task was presented using 3 mm green LEDs (70 mcd), the first as the central fixation LED mounted on a central fixation stand and the second as the peripheral target LED, which was attached to the tip of a robotic arm (Thermo CRS, Burlington, ON, Canada). The central fixation LED was positioned at eye level, 42 cm away from the chin rest and participant. The task was completed in the dark.

2.4. Visually-guided reaching task

Each trial began with the participant fixating their eyes on the central LED and their right index finger resting on the central fixation stand for a time interval between 2000 and 3000 ms, after which the central LED was extinguished. After a 200 ms gap, a peripheral target LED was presented to the right along the horizontal plane. The participant was instructed to "look and touch the target LED as accurately as possible at a comfortable speed." The target LED was presented for 2000 ms at a 10° or 15° visual angle (7.41 or 11.25 cm) from the central LED at random, but only trials with the 15° target were analyzed in this manuscript for simplicity. We chose a 15° visual angle due to equipment limitations for accurate eye-tracking and we used the 10° visual angle to introduce a choice to prevent memorization of the target location. We chose to analyze only the 15° target trials because these trials were more difficult than the 10° target trials, making them likely more sensitive to differences in behavior. Participants performed one block of 20 trials, 10 trials for each target LED location, to prevent fatigue while having enough trials to reach statistical significance according to pilot testing. Participants were given a short break after 10 trials and the lights were turned on to limit adaptation to the dark. Before the block of 20 trials, all participants completed practice trials until they could confidently perform the task correctly.

2.5. Data processing

The eye and upper limb data were processed using a custom MATLAB script (The MathWorks Inc., Natick, MA, USA). Eye and upper limb position data were filtered using a 20 Hz low-pass second-order, zero-phase Butterworth filter. The filtered position data were differentiated to calculate velocity. Tangential velocity was calculated in 2 dimensions for the eye movement data and in 3 dimensions for upper limb movement data.

TABLE 2 Clinical stimulation settings for the participants in the STN-DBS effects analysis.

ID	Left stimulator clinical settings					Right stimulator clinical settings				
	Amp (V or mA)	Freq (Hz)	PW (μs)	+ Contact	− Contact	Amp (V or mA)	Freq (Hz)	PW (μs)	+ Contact	− Contact
1	3.0*	130	60	1	0	4.0*	130	60	10	9
2	2.4	130	60	Case	2abc	2.2	130	60	Case	10abc
3	3.0*	125	60	1	2	3.2*	125	60	Case	9
4	2.5*	130	60	0	2, 3	2.9*	130	90	11	9
5	2.9	160	90	Case	3ac	2.0	130	60	Case	10abc
6	2.4	130	60	Case	3abc	3.2	130	90	Case	10abc
7	2.9	130	60	Case	3abc	2.9	130	60	Case	10abc
8	3.0	130	60	Case	2abc	3.1	130	60	Case	10ab
9	2.1	130	60	Case	2c	2.7	130	60	Case	10c
10	3.8	130	60	Case	2c, 4	2.8	130	60	Case	10abc
11	3.6	130	60	Case	2c	2.5	180	60	Case	10abc

The above left and right settings were used for bilateral STN-DBS testing.

* Indicates that the participant had constant voltage stimulation and the amplitude value is in volts. All other participants had constant current stimulation and the amplitude value is in milliamperes. Amp, amplitude; Freq, frequency; Hz, hertz; μs, microsecond; mA, milliamperes; − Contact, negative contact; + Contact, positive contact; PW, pulse width; V, volts. Those with constant current stimulation had segmented electrodes, which are represented by the segment names a, b, and c.

Using the eye and upper limb position data and the tangential velocity data, an approximate estimate of the eye and upper limb movement onset and offset was marked using visual inspection to create a region of interest in time. We computed eye and upper limb peak velocities within this region of time. From the peak velocities, we identified the first time point when velocity went below 5% of the peak velocity, which was defined as the eye or upper limb movement onset. Saccade latency and reach RT were defined as the time difference between target LED onset and the algorithmically identified movement onset of the saccade or reach. During visual inspection, if it was clear the trial was not performed correctly, it was marked invalid. For instance, if the participant moved their eyes or upper limb prior to the presentation of the target LED or if they did not complete the reach in the allotted time. All trials marked invalid were excluded.

After visual inspection, trials were further excluded based on predetermined criteria: (1) saccade latency was < 90 ms (Munoz et al., 1998) or > 1000 ms, (2) reach RT was < 200 ms or > 1000 ms, or (3) reach RT occurred > 500 ms before saccade latency. Based on visual inspection of the data, trials were excluded as outliers if reach peak velocity was > 1 m/s or reach end point error was > 5 cm. Our outcome variables were saccade latency, reach RT, saccade peak velocity, and reach peak velocity.

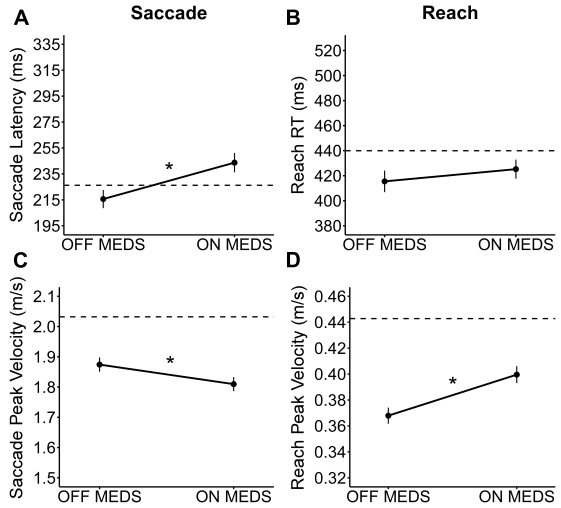

FIGURE 1
The medication effect on saccades and reaching. The observed medication effect on **(A)** saccade latency, **(B)** reach RT, **(C)** saccade peak velocity, and **(D)** reach peak velocity. The plots show the mean medication effect and standard errors, with observed means from healthy controls presented for reference (dashed line). * Indicates that the medication effect was statistically significant ($p < 0.05$).

2.6. Statistical analysis

Linear mixed-effect regression models were used to assess each of the saccade and reach outcomes. For the medication analysis, the fixed effect was medication condition (OFF and ON medication). For the STN-DBS analysis, the fixed effect was STN-DBS condition (OFF and ON bilateral STN-DBS). The random effect was participant in both analyses. To meet the distributional assumptions for mixed modeling, if the observed data was right skewed, the data was transformed using a log function. This occurred for saccade latency, reach RT, and reach peak velocity. If the observed data was left skewed, the data was transformed using a squared function. This was the case for saccade peak velocity. The statistics presented are in log or squared scales, along with the estimated difference transformed back to the original scale (Est diff_{BT}). The relationship between saccade latency and reach RT was assessed across medication conditions, across STN-DBS conditions, and in the healthy controls using mixed-effect regression models. Mixed models were also used to assess the interaction between the treatment and saccade latency effects on reach RT. The significance of the results was identical between the original scale and the log transformation scale, so we present the data and statistics in the original scale for ease of interpretation. All statistical analyses were performed using SAS® (version 9.4, SAS Institute, Cary, NC, USA).

3. Results

3.1. Medication effect

Medication significantly increased saccade latency [Est $\text{diff}_{BT} = 25.98$ ms; $F_{(1,542)} = 17.50$; $p < 0.001$; **Figure 1A**] but had no statistically significant effect on reach RT [Est $\text{diff}_{BT} = 13.96$ ms; $F_{(1,542)} = 2.96$; $p = 0.086$; **Figure 1B**] compared to OFF medication. Additionally, medication significantly decreased saccade peak velocity [Est $\text{diff}_{BT} = -0.04$ m/s; $F_{(1,542)} = 4.75$; $p = 0.030$; **Figure 1C**] but significantly increased reach peak velocity [Est $\text{diff}_{BT} = 0.03$ m/s; $F_{(1,542)} = 23.00$; $p < 0.001$; **Figure 1D**] compared to OFF medication. Observationally, with medication, the mean saccade latency and peak velocity became further from healthy control means, while mean reach peak velocity became closer to healthy control means.

3.2. Bilateral STN-DBS effect

Bilateral STN-DBS significantly decreased saccade latency [Est $\text{diff}_{BT} = -38.89$ ms; $F_{(1,159)} = 7.75$; $p = 0.006$; **Figure 2A**] but had no statistically significant effect on reach RT [Est $\text{diff}_{BT} = -29.93$ ms; $F_{(1,159)} = 2.91$; $p = 0.090$; **Figure 2B**] compared to OFF STN-DBS. Additionally, bilateral STN-DBS significantly increased saccade peak velocity [Est $\text{diff}_{BT} = 0.09$ m/s; $F_{(1,159)} = 4.20$; $p = 0.042$; **Figure 2C**] and significantly increased reach peak velocity [Est $\text{diff}_{BT} = 0.03$ m/s; $F_{(1,159)} = 6.48$; $p = 0.012$; **Figure 2D**] compared to OFF STN-DBS. Observationally, all three statistically significant findings resulted in performance changes with STN-DBS that became closer to healthy control performance.

3.3. Saccade latency effect on reach RT

Since the direction of change in mean reach RT followed the change in mean saccade latency for both treatments, we wanted to determine the relationship between saccade latency and reach RT. Saccade latency had a significant positive relationship with reach RT across the OFF and ON data of the participants in the

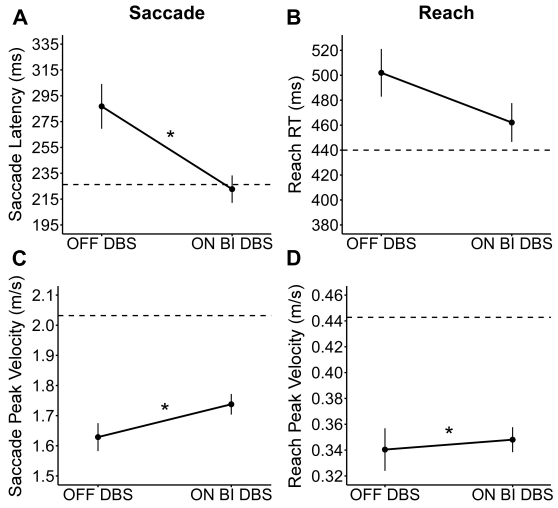

FIGURE 2
The bilateral STN-DBS effect on saccades and reaching. The observed STN-DBS effect on **(A)** saccade latency, **(B)** reach RT, **(C)** saccade peak velocity, and **(D)** reach peak velocity. The plots show the mean STN-DBS effect and standard errors, with observed means from healthy controls presented for reference (dashed line). Participants were OFF medication during OFF and ON bilateral STN-DBS testing. * Indicates that the bilateral STN-DBS effect was statistically significant ($p < 0.05$).

medication analysis [$\beta = 0.452$; estimated intraclass correlation coefficient (ICC) = 30.58%; $p < 0.001$; **Figure 3A**] and of the participants in the STN-DBS analysis [$\beta = 0.389$; ICC = 43.26%; $p < 0.001$; **Figure 3B**]. To determine if this relationship was affected by treatment, we also determined whether there was an interaction between the treatment and saccade latency effects on reach RT. There was no interaction between either medication condition and saccade latency ($p = 0.171$) or STN-DBS condition and saccade latency ($p = 0.211$). Finally, the positive relationship between saccade latency and reach RT was also seen in the healthy controls ($\beta = 0.484$; ICC = 65.74%; $p < 0.001$; **Figure 3C**). In the vast majority of trials, saccade initiation occurred before reach initiation for the participants in the medication analysis (**Figure 3D**), participants in the STN-DBS analysis (**Figure 3E**), and healthy controls (**Figure 3F**).

4. Discussion

We investigated the effects of antiparkinson medication and bilateral STN-DBS on visually-guided saccades and reaching movements during a visually-guided reaching task. Notably, this is the first report of both the medication and STN-DBS effects on the eye and upper limb movements during the same task. We have three key findings. First, antiparkinson medication had an adverse effect on saccade performance and a beneficial effect on one aspect of reach performance. Antiparkinson medication increased saccade latency, decreased saccade peak velocity, and increased reach peak velocity. Second, STN-DBS had a beneficial effect on saccade performance and a beneficial effect on one aspect of reach performance. Bilateral STN-DBS decreased saccade latency, increased saccade peak velocity, and increased reach peak velocity.

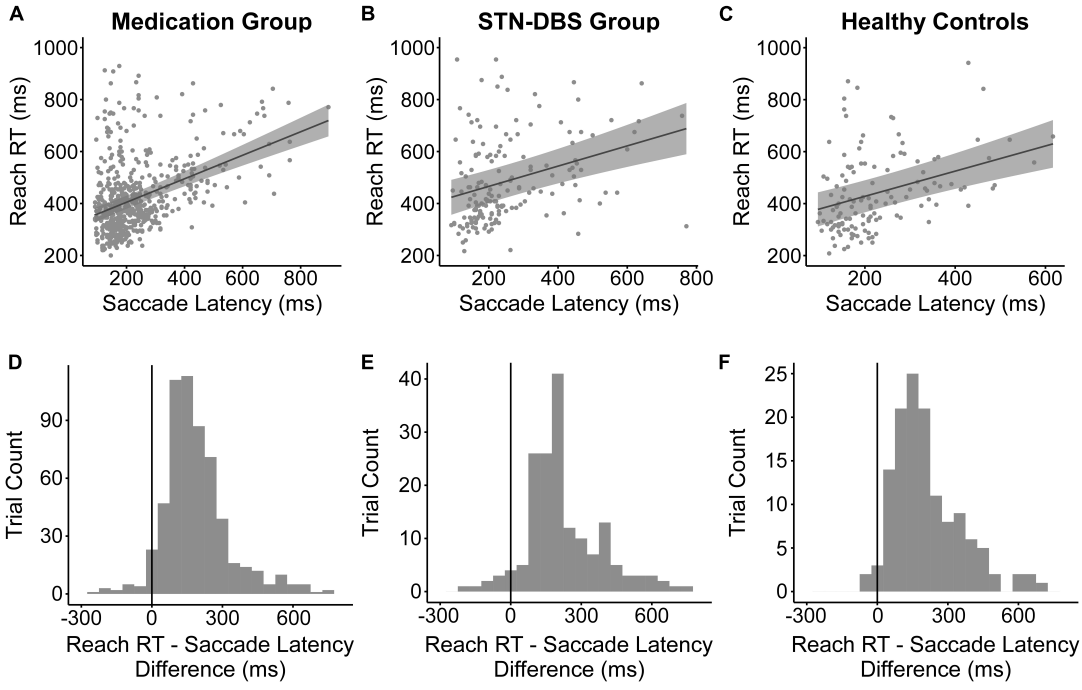

FIGURE 3
Relationship between saccade latency and reach reaction time. The relationship was significant for the data analyzed for the **(A)** medication group, **(B)** STN-DBS group, and **(C)** healthy controls. The plots depict the model-estimated relationship (solid black line) and 95% confidence interval (gray shaded area). The observed trial-level data are overlaid onto the plots (gray filled circles). The histograms show the difference in time between the reach RT and saccade latency for the **(D)** medication group, **(E)** STN-DBS group, and **(F)** healthy controls. All values over zero show that saccade initiation occurs before reach initiation.

Third, we confirmed that there was a positive relationship between saccade latency and reach RT across treatment groups and healthy controls, in which saccade initiation preceded limb initiation. Importantly, the positive relationship remained unaffected by treatment. Finally, we discuss the possible parallel mechanisms underlying the similar effects of medication and STN-DBS on reach peak velocity and the possible unique mechanisms underlying the differential effects of medication and STN-DBS on saccade performance.

4.1. Differential effects of medication on saccade and reach performance

We found that antiparkinson medication adversely impacted saccade performance and benefitted one aspect of reach performance (**Figure 1**). Our findings confirmed our prediction that antiparkinson medication would increase saccade latency. Our recent study and other previous studies have shown that medication increases saccade latency during a saccade only task (Müller et al., 1994; Michell et al., 2006; Hood et al., 2007; Dec-Ćwiek et al., 2017; Lu et al., 2019; Waldthaler et al., 2019; Munoz et al., 2022). The effect of medication on saccade peak velocity has been less established. Three previous studies have found no statistically significant effect on saccade peak velocity (Rascol et al., 1989; Dec-Ćwiek et al., 2017; Lu et al., 2019), but, observationally, 2 of the 3 showed a slight decrease in peak velocity with medication during the visually-guided saccade task (Dec-Ćwiek et al., 2017; Lu et al., 2019). The third study did not show a slight decrease, possibly because of the small medication dosage given to the participants (Rascol et al., 1989). Our recent study found a statistically significant decrease in peak velocity with medication on the visually-guided saccade task (Munoz et al., 2022). In the present study, we extended previous saccade findings. Medication increases saccade latency and decreases saccade peak velocity not only during a saccade task, but also in a task requiring eye-hand coordination.

Additionally, our findings confirmed our hypothesis that antiparkinson medication would significantly increase reach peak velocity, while increasing reach peak velocity. The beneficial medication effects on upper limb velocity are well known, and we replicate this beneficial effect (Baroni et al., 1984; Berardelli et al., 1986; Johnson et al., 1994; Castiello et al., 2000; Kelly et al., 2002; Camarda et al., 2005; Negrotti et al., 2005; Schettino et al., 2006). This finding, in addition to a clear increase in MDS-UPDRS Part III score, made it clear that a 12-h withdrawal period was sufficient for our participants to be in an "off state," even those on longer-acting medications, like dopamine agonists. Together, these findings suggest that medication has a differential effect on the oculomotor and skeletomotor systems.

4.2. Similar effects of bilateral STN-DBS on saccade and reach performance

We found that bilateral STN-DBS improved both saccade performance and one aspect of reach performance (**Figure 2**). Our findings confirmed our hypotheses that bilateral STN-DBS would significantly decrease saccade latency and increase saccade peak velocity compared to OFF stimulation. Previous studies have also reported that bilateral STN-DBS decreased saccade latency (Fawcett et al., 2007, 2010; Sauleau et al., 2008; Temel et al., 2008, 2009; Yugeta et al., 2010; Antoniades et al., 2012b,a, 2015; Dec-Ćwiek et al., 2017; Goelz et al., 2017; Bakhtiari et al., 2020) and increased saccade peak velocity (Nilsson et al., 2013) in a saccade only task. In addition, bilateral STN-DBS has improved saccadic eye movements during a more complex visual searching task (Tokushige et al., 2018). In the current study, we extend these findings and demonstrate that STN-DBS also has beneficial effects on saccades during a task requiring eye-hand coordination.

Additionally, we confirmed our prediction that STN-DBS would significantly increase reach peak velocity. This is similar to previously reported improvements in upper limb peak velocity (Vaillancourt et al., 2004; Dafotakis et al., 2008; Joundi et al., 2012; Tamás et al., 2016). However, it was surprising that we did not see a larger effect of STN-DBS on reach peak velocity. This was likely because our participants were instructed to move "at a comfortable speed" instead of as fast as possible. This guidance was necessary to prevent participants from hitting the robotic arm that presented the target. Another potential explanation is that the target amplitude was relatively small, only 15° or 11.25 cm away from center, meaning the reach was small. A smaller movement limits how fast a participant can move, even with the beneficial effects of stimulation. Overall, our data suggests that bilateral STN-DBS acts similarly on the oculomotor and skeletomotor systems. The effects of STN-DBS on these systems seem to be beneficial as stimulation brings performance of participants with PD closer to healthy control levels.

4.3. The relationship between saccade latency and reach RT

We found a positive relationship between saccade latency and reach RT in the medication group, the STN-DBS group, and in our healthy controls (**Figure 3**). This relationship was unaffected by medication and STN-DBS. The positive relationship between saccade latency and reach RT has previously been seen in reports on healthy populations (Prablanc et al., 1979; Herman et al., 1981; Biguer et al., 1982; Gielen et al., 1984; Fischer and Rogal, 1986). Specifically, the eyes typically lead the hands (Biguer et al., 1982). In the current study, the initiation of the saccade to the target preceded the initiation of the reach in over 96% of trials for the medication group and over 94% of trials for the STN-DBS group. Therefore, the previously reported positive relationship between saccade latency and reach RT in healthy controls persists in people with PD and remains unaffected by treatment.

The fact that the current study uses a task requiring eye-hand coordination may explain why we found a non-significant increase in reach RT with medication, whereas previous studies have shown a decrease. Simple RT studies have consistently reported that medication significantly (Montgomery and Nuessen, 1990) or non-significantly decreases RT (Velasco and Velasco, 1973; Bloxham et al., 1987; Pullman et al., 1988, 1990; Starkstein et al., 1989;

Jahanshahi et al., 1992; Fern-Pollak et al., 2004; Ingram et al., 2021). Even in more complex reaching tasks, in which upper limb RT was measured before a reach to one of multiple targets, medication still decreased RT either significantly (Zappia et al., 1994) or not significantly (Girotti et al., 1986). However, these previous studies did not require explicit eye-hand coordination to complete the task, whereas our task required eye-hand coordination to look and reach to a visual target. As saccade latency was prolonged by medication, it would follow that reach RT would be unable to decrease.

4.4. Potential mechanisms underlying the beneficial effects of medication and STN-DBS on upper limb peak velocity

We found that both medication and bilateral STN-DBS improved upper limb peak velocity, as would be expected. The two common pathophysiological models of PD, the rate model and the oscillation model, can both explain this benefit to upper limb peak velocity (David et al., 2020).

Without treatment, PD is characterized by slowness of movement, which is thought to be due to the loss of dopaminergic neurons in the substantia nigra pars compacta projecting to the striatum (Brooks et al., 1990). This results in decreased activity of the basal ganglia direct pathway and increased activity of the indirect pathway (Albin et al., 1989). Combined, the imbalance between the basal ganglia pathways increases the inhibitory activity of the basal ganglia output nuclei, the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr) (Albin et al., 1989). Therefore, there is excessive inhibition from the basal ganglia output nuclei to downstream targets, such as thalamus, which then results in decreased activation of cortical areas (Albin et al., 1989) and disruption of the motor network (Bologna et al., 2020). It is thought that both antiparkinson medication and STN-DBS reduce the excessive inhibition from the basal ganglia onto the thalamus and reduce the resulting decreased cortical activation, with medication restoring dopamine levels in the striatum and STN-DBS decreasing the overactivity of the indirect pathway. In support of this, positron emission tomography (PET) studies looking at the effects of medication (Jenkins et al., 1992; Rascol et al., 1992, 1994) and STN-DBS (Limousin et al., 1997; Ceballos-Baumann et al., 1999; Grafton et al., 2006) have found that both treatments increase metabolic activity in the motor cortices, especially the supplementary motor cortex. The increased activation of supplementary motor cortex has been correlated with improvement in akinesia with medication (Jenkins et al., 1992) and STN-DBS (Limousin et al., 1997; Ceballos-Baumann et al., 1999), which could explain our beneficial effect on peak velocity.

Additionally, without treatment, PD is also characterized by excessive beta band synchronization throughout the motor loop at rest, both between neurons and in local field potentials (Brown et al., 2001; Levy et al., 2002; Hammond et al., 2007). A proposed explanation of the motor dysfunction in PD is that the excessive tonic beta synchronization prevents the phasic beta suppression that is needed to execute a planned movement (Brittain and Brown, 2014). Medication has been reported to suppress this excessive beta band synchronization at rest (Brown et al., 2001; Levy et al., 2002; Priori et al., 2004; Kühn et al., 2006; Ray et al., 2008), which has been associated with improvement in bradykinesia, akinesia, and rigidity (Kühn et al., 2006; Ray et al., 2008). STN-DBS has also been reported to suppress excessive beta band synchronization at rest in the STN (Eusebio et al., 2011) and throughout the motor loop (Brown et al., 2004; Silberstein et al., 2005). STN-DBS improvement in bradykinesia and rigidity correlates with beta suppression at the cortex during STN-DBS (Silberstein et al., 2005) and following the cessation of STN-DBS (Kühn et al., 2008). The similar mechanistic effects of medication and STN-DBS associated with the beneficial motor effects could also contribute to the reported increase in upper limb peak velocity.

4.5. Potential mechanisms underlying the opposing effects of medication and STN-DBS on saccade latency and peak velocity

We found that medication worsened saccade performance by increasing latency and decreasing peak velocity, while STN-DBS improved saccade performance by decreasing latency and increasing peak velocity. In previous studies showing that STN-DBS improves visually-guided saccade performance, the proposed mechanisms are similar to those thought to underlie the improvement in the skeletomotor system after STN-DBS (Sauleau et al., 2008; Temel et al., 2009; Fawcett et al., 2010; Yugeta et al., 2010; Nilsson et al., 2013; Goelz et al., 2017). The worsened visually-guided saccade performance in PD is thought to be due to excessive inhibition on the superior colliculus (Albin et al., 1989; Terao et al., 2011) from the SNr (Hikosaka et al., 2000). STN-DBS reduces the activity of the SNr (Benazzouz et al., 1995; Maltête et al., 2007), which suggests that the superior colliculus would be released from this excessive inhibition. The benefit to saccade performance could also be explained by STN-DBS reducing the excessive beta band oscillations in the basal ganglia, returning the superior colliculus to normal activity levels, and facilitating eye movement (Yugeta et al., 2010). Previous studies have argued that the oscillation model better describes the observed changes in saccade performance in PD and with STN-DBS compared to the rate model (Yugeta et al., 2010). However, as discussed previously, it has been reported that medication also reduces the beta band synchronization in the STN (Brown et al., 2001; Levy et al., 2002; Priori et al., 2004; Kühn et al., 2006; Ray et al., 2008). Therefore, other mechanisms must be contributing to this difference in saccade performance.

It is possible that medication is also acting on other brain areas to counteract the normalization of beta oscillations. As we suggested in a prior publication (Munoz et al., 2022), medication may impair visually-guided saccadic function by overdosing dopaminergic brain regions that are not dopamine depleted in PD. One potential region is the superior colliculus, which has been found to receive dopaminergic projections from the zona incerta and have D2-expressing neurons (Bolton et al., 2015). When dopamine was washed onto the D2-expressing superior colliculus neurons, neuronal activity was suppressed (Bolton et al., 2015). In a different animal model, similar superior colliculus activity suppression resulted in inhibited behavioral responses, such

as decreased orientation to stimuli (Glagow and Ewert, 1997). Relatedly, a study examining posterior subthalamic area DBS (PSA DBS) found that, unlike STN-DBS, saccade amplitude and peak velocity were decreased with stimulation (Bangash et al., 2019). It was likely that the zona incerta was being stimulated with PSA DBS (Bangash et al., 2019), which could subsequently inhibit the downstream superior colliculus potentially via an excessive release of dopamine onto the superior colliculus. Taken together, these studies suggest the possibility that the dopamine overdose of the superior colliculus, via medication or stimulation of the zona incerta, could result in worsened saccade performance. Another potential overdosed region is the prefrontal cortex, resulting in increased inhibition from the prefrontal cortex onto the superior colliculus (Hood et al., 2007). Increased dopamine levels in the prefrontal cortex have been shown to result in prolonged saccade latency (Cameron et al., 2018). Additionally, increased inhibition from the frontal cortex has been suggested to inhibit reflexive saccades to allow for sufficient processing time to make a planned saccade (Terao et al., 2013) or to detrimentally increase the focusing of attention, making attention shifting more difficult (Cameron et al., 2018). Conversely, it has been suggested that bilateral STN-DBS may improve visual attention (Tokushige et al., 2018). Dopamine overdose of both the superior colliculus or the frontal cortex could result in an increase in visually-guided saccade latency and a decrease in saccade peak velocity. The overdosing of subcortical and cortical regions is not mutually exclusive and could be occurring simultaneously.

5. Conclusion

Using a visually-guided reaching task requiring eye and upper limb movements, we demonstrate that antiparkinson medication adversely impacts saccade performance, while it improves reaching performance. Additionally, we demonstrate that bilateral STN-DBS improves both saccade and reaching performance. Our findings highlight the importance of assessing multiple effectors simultaneously to evaluate how the parkinsonian brain may be affected by treatment. Crucially, the similar and differential effects of antiparkinson medication and STN-DBS on the oculomotor and skeletomotor systems suggest parallel and unique mechanisms of action of antiparkinson medication and STN-DBS. While medication and STN-DBS may impact the basal ganglia circuitry similarly, medication may also overdose other dopaminergic areas resulting in worsened saccade performance.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Northwestern University Institutional Review Board and the Rush University Medical Center Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MM, LG, DC, and FD contributed to conceptualization and/or methodology of the study. MM, YR, LG, and FD contributed to project administration. GP, LV, SS, and JR provided resources needed for the study. MM, RA, YR, QD, LG, and FD assisted with data collection and/or data processing. MM performed the formal analysis and wrote the original draft of the manuscript. DC and FD supervised the study and the formal analysis. All authors reviewed, edited, and approved the submitted version of the article.

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Conflict of interest

GP received grant support from National Institute of Neurological Disorders and Stroke, and consulting fees from Guidepoint, Kyowa Kirin. LV receives research support from NIH; receives research support, is on the advisory board of, and consults for Abbott, AbbVie, and Avion; receives research support from and consults for Boston Scientific; receives research support from and is on the advisory board for Biogen; and receives research support from Medtronic, Neuroderm, and Prilenia Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Novel utilization of deep brain stimulation in the pedunculopontine nucleus with globus pallidus internus for treatment of childhood-onset dystonia

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Introduction: Deep brain stimulation (DBS) is a well-documented therapy for dystonia utilized in many adult and pediatric movement disorders. Pedunculopontine nucleus (PPN) has been investigated as a DBS target primarily in adult patients with dystonia or dyskinesias from Parkinson's disease, showing improvement in postural instability and gait dysfunction. Due to the difficulty in targeting PPN using standard techniques, it is not commonly chosen as a target for adult or pediatric pathology. There is no current literature describing the targeting of PPN in DBS for childhood-onset dystonia.

Methods: Two pediatric and one young adult patient with childhood-onset dystonia who underwent DBS implantation at our institution were identified. Patient 1 has Mitochondrial Enoyl CoA Reductase Protein-Associated Neurodegeneration (MEPAN) syndrome. Patient 2 has Glutaric Aciduria Type 1 (GA1). Patient 3 has atypical pantothenate kinase-associated neurodegeneration (PKAN). PPN was identified as a potential target for these patients due to axial or orofacial dystonia. Pre- and post-operative videos taken as part of routine clinical assessments were evaluated and scored on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and Barry-Albright Dystonia Scale (BADS). All patients had permanent electrodes placed bilaterally in PPN and globus pallidus internus (GPi). A Likert scale on quality of life was also obtained from the patient/parents as applicable.

Results: Significant programming was necessary over the first 3–12 months to optimize patients' response to stimulation. All patients experienced at least a 34% improvement in the BFMDRS score. Patients 2 and 3 also experienced an over 30% improvement in BADS score. All patients/parents appreciated improvement in quality of life postoperatively.

Discussion: Deep brain stimulation in PPN was safely and successfully used in two pediatric patients and one young adult patient with childhood-onset dystonia. These patients showed clinically significant improvements in BFMDRS scoring post operatively. This represents the first reported DBS targeting of PPN in pediatric patients, and suggests that PPN is a possible target for pediatric-onset dystonia with axial and orofacial symptoms that may be refractory to traditional pallidal stimulation alone.

KEYWORDS

dystonia, pediatrics, pedunculopontine nucleus, deep brain stimulation, orofacial dyskinesia, stereotaxy

1. Introduction

Deep brain stimulation (DBS) is a surgical technique commonly used to treat medically refractory dystonia in children and adults. Initially approved for utilization in treatment of Parkinson's disease (PD), DBS was approved for treatment of dystonia in 2003 (U.S. Food and Drug Administration, Center for Devices and Radiological Health, 2003). Dystonia can be classified as primary, occurring without other brain abnormalities, or secondary, when it is associated with central nervous system injury due to a wide variety of potential causes. The treatment efficacy of DBS is well-established for certain genetic pediatric-onset primary dystonia, and current literature shows selection of the globus pallidus internus (GPi) as the primary target for stimulation generally results in some degree of improvement in motor symptoms (Kupsch et al., 2006; Ostrem and Starr, 2008). However, treatment of other pediatric-onset dystonias with DBS is rarely as straightforward, since the multitude of possible origins can result in several different clinical presentations of dystonia. The identification of optimal stimulation targets for these dystonic conditions remains an open question in the field since the reported outcomes on use of GPi DBS are limited in scope and consistency (Ostrem and Starr, 2008).

Several additional possibilities for DBS targets have been identified and are now commonly used, including subthalamic nucleus (STN), ventrolateral thalamus (VL), ventral intermediate nucleus of the thalamus (VIM), and ventralis oralis anterior (Voa) and posterior (Vop) nuclei of the thalamus (Ostrem and Starr, 2008; Vitek et al., 2011). Use of these targets in treatment of dystonia has yielded varied results, suggesting that the specified thalamic and basal ganglia targets are suitable for consideration, but that optimal targets for stimulation may be patient specific (Krack and Vercueil, 2001; Katsakiori et al., 2009). It is also likely that optimal targets may have to be identified based on the specific distribution and symptomatology of dystonia. One key example is in patients presenting with orofacial and axial symptoms. Although stimulation in standard pallidal targets was able to elicit some improvement in orofacial deficits in subjects with secondary dystonia, the results were not comparable to the level of benefit achieved in treatment of primary dystonia (Castelnau et al., 2005). A similarly dissatisfactory result is seen in patients with PD who display axial motor deficits, which are poorly responsive to the commonly utilized targets of STN and GPi (Thevathasan et al., 2018). The lack of response of these deficits to standard targets has motivated the search for novel DBS targets.

Deep brain stimulation in the pedunculopontine nucleus (PPN) was first identified as an experimental therapy to treat axial motor symptoms in PD, since PPN is a major component of the mesencephalic locomotor region and is thought to play a role in gait and production of movement (Thevathasan et al., 2018). Although initially an exciting prospect, the reported outcomes on PPN DBS for PD patients were largely inconclusive (Thevathasan et al., 2018). Despite this anticlimactic result in the PD population, there is reason to believe that PPN DBS could provide therapeutic benefit in the treatment of other motor disorders, such as secondary dystonia. Although the specific mechanisms of dystonia are unknown, it is often characterized as a network disorder involving the basal ganglia-cerebello-thalamo-cortical circuit (Ostrem and Starr, 2008; Su et al., 2022).

The PPN is a brainstem structure located in the caudal mesencephalic tegmentum, and it displays widespread reciprocal anatomical connections to the cerebral cortex, thalamus, basal ganglia, motor regions of the brainstem, and spinal cord (Alam et al., 2011; Rowe et al., 2016; Nowacki et al., 2019). The PPN is separated into the rostral and caudal sections with the former containing mainly GABAergic neurons, the latter containing mainly glutamatergic neurons, and intermingled cholinergic neurons throughout the entire structure (Nowacki et al., 2019). The PPN is anatomically and functionally relevant to dystonia due to its complex ascending connections with the basal ganglia and cerebellum, which are thought to play a role in selection and coordination of movements (Su et al., 2022). The PPN is also believed to have descending connections to cranial nerve nuclei V, VII, and XII, as well as to effectors in the spinal cord (Su et al., 2022). These descending projections to areas driving tongue, facial, and trunk musculature allow us to identify PPN as an interesting potential target for treatment of orofacial and axial features of dystonia.

The complex and widespread connectivity of PPN suggests that it is also implicated in several non-motor functions such as regulation of the sleep–wake cycle and attentional networks such as the reticular activating system (Garcia-Rill et al., 2015; Nowacki et al., 2019). This raises the concern for possible nonmotor benefits and side effects. Possible non-motor effects of PPN DBS include promotion of rapid eye movement (REM) sleep, related to the enhancement of the acetylcholine releasing subpopulation of neurons within PPN that may affected by specific frequencies of stimulation (Rye, 1997). Increased REM sleep has been observed in the Parkinson's disease population with PPN stimulation, though without a change in the

presence of REM sleep behavior disorder or overall total sleep time, suggesting involvement of multiple pathways (Lim et al., 2009). Additionally, the proximity of PPN to the pontine micturition center suggests that PPN DBS may induce undesirable urinary side effects, previously reported in PD patients (Aviles-Olmos et al., 2011; Thevathasan et al., 2018). Other previously reported adverse effects of PPN DBS include contralateral paresthesia, sensation of pain, oscillopsia, and limb myoclonus (Nowacki et al., 2019).

The vast involvement of the PPN in central nervous system anatomical and functional networks, in conjunction with its relatively small size and the difficulty involved in targeting it using standard neurosurgical techniques suggest that PPN DBS could very well be a double-edged sword (Welter et al., 2015). While it shows promise as an emerging therapy, it is clear that optimal targeting of PPN to increase benefit and diminish side effects will depend heavily on methodological considerations such as electrode size, stimulation voltage and frequency, and the use of stimulation cycling parameters. We report the response of three subjects, two pediatric and one young adult, with dystonia of heterogeneous etiologies receiving combined stimulation in GPi and PPN. To the best of our knowledge, there is no current literature describing the targeting of PPN in DBS for childhood-onset dystonia.

2. Materials and methods

2.1. Subjects

Two pediatric and one young adult patient with childhood-onset dystonia who underwent DBS implantation at our institution were identified. All three patients were previously diagnosed with dystonia by a pediatric movement disorder specialist (TDS) based on established criteria (Albanese et al., 2013). All had failed standard pharmacotherapy at adequate dosing (Luc and Querubin, 2017) as well as botulinum toxin injections.

Patient 1 is a male with Mitochondrial Enoyl CoA Reductase Protein-Associated Neurodegeneration (MEPAN) syndrome diagnosed by whole genome sequencing. He was 10 years old at the time of DBS placement. His predominant symptoms were axial and appendicular dystonic posturing. He had very limited speech due to severe dysarthria, but was able to utilize an assistive communication device and was performing at grade level. Due to axial posturing he was unable to ambulate with or without support, sit comfortably in his wheelchair, or independently perform many activities of daily living including feeding himself.

Patient 2 is a male with glutaric aciduria type I (GA1) who had an initial metabolic crisis as an infant prior to diagnosis by genetic testing. His predominant symptoms were orofacial dyskinesias and axial posturing that were interfering with his ability to sit comfortably in a wheelchair or initiate sleep. He was 8 years old at the time of implantation. He was appreciated to have significant cognitive delays and limited communication.

Patient 3 is a 23 year old male diagnosed with atypical pantothenate kinase-associated neurodegeneration (PKAN). He was noted to have normal cognition and communicated by speech despite severe dysarthria. His predominant concerns were orofacial and oropharyngeal dystonia interfering with eating and speech. He had multiple episodes of choking requiring the Heimlich maneuver at home. Despite extensive discussions with multiple subspecialists at multiple institutions he refused consideration of a gastronomy tube and instead requested consideration for deep brain stimulation to address the dystonic spasms limiting his oral intake.

Patients or parents of minor patients consented to surgical procedures according to standard hospital consent procedures. They also consented or assented as appropriate to HIPAA authorization for research use of protected healthcare information and IRB-approved consent for videotaping and scale scoring of video recordings.

2.2. Surgical procedure

As all three patients had dystonia due to a condition with either known inadequate response to pallidal stimulation alone (GA1, atypical PKAN) or no known response to DBS (MEPAN), it was elected to perform a previously described staged surgical target identification method (Sanger et al., 2018a,b; MacLean et al., 2021, 2023). All subjects were initially implanted with 12 depth electrodes (six bilaterally) in possible targets of pallidum, thalamus, subthalamic nucleus, and PPN. PPN was identified as providing optimal benefit in conjunction with globus pallidus internus (GPi) stimulation on all three patients' major debilitating dystonic symptoms during a 4–6 day inpatient hospitalization with externalized depth electrodes in which stimulation of various areas was trialed to assess clinical response. PPN was specifically targeted in these patients based on the literature regarding benefits associated with stimulation in PD patients and the lack of response of orofacial and axial dystonia to typical pallidal and thalamic targets. All subjects also concurrently had leads implanted in bilateral GPi based on their response to test stimulation.

Stereotaxy for both depth and permanent electrodes was performed using the ROSA surgical robot with guidance from ONE™ software (Zimmer Biomet, Montpellier, France). Targeting was performed using standard surgical anatomical Schaltenbrand-Wahren atlas locations relative to the AC-PC line. Initially, PPN was targeted based on standard ACPC coordinates (Thevathasan et al., 2018), however targets were subsequently adjusted based on each patient's individual anatomy on a high-resolution pre-operative MRI. The coordinates of each patient and the standard coordinates are noted in Table 1. Targeting was confirmed by intraoperative fluoroscopy and postoperative CT.

Patient 1 was implanted with bilateral Sensight1.5 electrodes (Medtronic Inc., Minneapolis, MN, United States) while patients 2 and 3 were each implanted with bilateral Sensight0.5 electrodes (Medtronic Inc.) in PPN to allow more precise stimulation patterns due to closer spaced stimulation contacts, based on the response of patient 1. All patients were concurrently implanted with two bilateral Sensight1.5 electrodes (Medtronic Inc.) in GPi. Given the utilization of segmented contacts on electrodes (in the two medial contacts of the four contact electrodes), adjustments were also made to ensure segmented contacts were in the targeted region. Trajectories of GPi electrodes were adjusted to allow for both leads in each hemisphere to exit through the same burr hole. Two weeks following placement of permanent electrodes, B34000 Sensight extensions (Medtronic Inc.) were connected to the intracranial electrodes and tunneled subcutaneously to implanted pulse generators (Medtronic Activa RC) placed in the chest. Homologous leads were directed to the same pulse generator (i.e., both PPN electrodes to the right generator).

2.3. Scales

All patients were assessed utilizing the Burke-Fahn-Marsden Dystonia Rating Scale (Burke et al., 1985; BFMDRS) and Barry-Albright Dystonia Scale (Barry and Vanswearingen, 1999; BADS) prior to surgery and at least 3 months postoperatively. Assessment was made by video review by a single clinician both preoperatively and postoperatively and then confirmed independently by a second clinician. Agreement from both scores was required for validation. Videos could not be blinded as patients showed visible effects of aging and surgical interventions.

TABLE 1 ACPC coordinates of PPN and GPi electrodes relative to mid-commissural point.

	Right PPN electrode	Left PPN electrode	Right GPi electrode	Left GPi electrode
Standard	$x = 6.5$	$x = -6.5$		
	$y = -15$	$y = -15$		
	$z = -14$	$z = -14$		
Patient 1	$x = 4.04$	$x = -3.29$	$x = 21.45$	$x = -15.85$
	$y = -17.21$	$y = -16.78$	$y = 5.19$	$y = 7.95$
	$z = -13.04$	$z = -16.74$	$z = -4.90$	$z = -4.01$
Patient 2	$x = 2.08$	$x = -4.64$	$x = 16.33$	$x = -15.31$
	$y = -14.91$	$y = -15.94$	$y = 4.27$	$y = 1.32$
	$z = -12.34$	$z = -15.93$	$z = -1.64$	$z = -1.67$
Patient 3	$x = 5.08$	$x = -5.68$	$x = 11.68$	$x = -13.02$
	$y = -18.67$	$y = -16.12$	$y = 6.22$	$y = 8.33$
	$z = -14.81$	$z = -14.02$	$z = 0.48$	$z = 2.29$

2.4. Stimulation parameters

At the time of generator placement low voltage stimulation was initiated on single circumferential monopolar contacts in GPi (1 v) and PPN (0.2 v) bilaterally. Contacts were selected based on location within the targeted structure by merge of the postoperative CT scan with a preoperative high-resolution MRI, shown in Figure 1. The patients were seen at 2 and 4 weeks postoperatively for initial mapping, followed by visits every 1–4 weeks for further programming.

2.4.1. Mapping

For mapping of PPN, all stimulation was initially turned off for 15 min. PPN stimulation was then reinitiated unilaterally with each contact including segmented contacts activated individually in monopolar stimulation. Initial stimulation was performed at 0.1 v, 40 Hz, and 60 μs. Benefits and side effects were noted by the examiner, family, and patient (when able) and voltage was gradually increased in 0.1 v increments to a maximum of 2 v or when side effects were appreciated. It was noted that stimulation provided ipsilateral and contralateral effects as well as truncal effects that were difficult to localize. A 2 min wash-out period was utilized between contacts to mitigate confounding effects, as well as a 10 min wash-out period

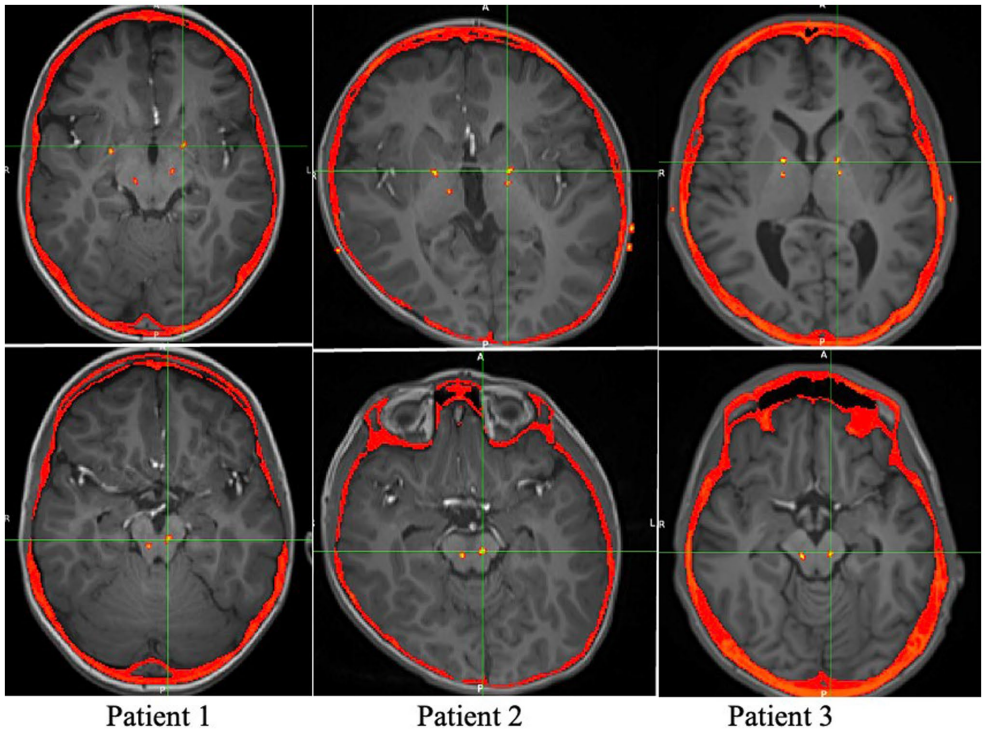

FIGURE 1
Axial views of the postoperative CT overlaid on the preoperative MRI, showing the locations of the Medtronic leads.

between electrodes. The patients' PPN electrodes were then reprogrammed with a combination of beneficial contacts at the most clinically effective voltage in monopolar mode. GPi electrode stimulation was left unchanged during this visit.

Approximately 2 weeks following mapping of the PPN electrodes, the patient returned to clinic for mapping of the pallidal electrodes. Due to possible additive effects between PPN and GPi stimulation, the mapping of GPi was performed with the patient on their previous PPN stimulation settings. GPi mapping was performed unilaterally with each contact probed beginning at 0.2 v, 185 Hz, and 90 μs, with gradual increases by 0.1 v to a maximum of 4 v or when side effects were appreciated. Given the neuroanatomy and previous known response to circumferential stimulation in GPi (Gelineau-Morel et al., 2022), segmented contacts were not initially explored for mapping. It has been noted by the clinicians that while the effects of GPi stimulation are best seen longitudinally, initial effects on dystonia could be appreciated by the clinician, patient, and family. A wash out period of 5 min without stimulation was given between contacts and 30 min between electrodes. Effects of unilateral stimulation were predominantly on the contralateral side of the body. The patient was then reprogrammed with the most effective monopolar pallidal stimulation contacts at the most clinically effective frequency. As none of the three patients experienced significant worsening of dystonia interim to this appointment their PPN stimulation was left unchanged at this time.

2.4.2. Programming

Following mapping visits, the patients were then seen every 1–4 weeks for further programming to optimize response. For the first 3 months, minimal changes were made to GPi except to gradually increase voltage as tolerated to therapeutic level of 3 v given longitudinal effects associated with pallidal stimulation. If significant side effects were appreciated, monopolar stimulation was often switched to bipolar or pulse width was decreased to limit current spread.

During the initial months of programming, focus was given to PPN. It was appreciated in all subjects that PPN stimulation was initially noted to have a transitory response on axial posturing as well as orofacial dyskinesias with any stimulation on beneficial contacts, but then with re-emergence of these concerns after several days. Patients 1 and 2 both experienced transient significant improvement in axial posturing for 48–72 h after programming visits with subsequent worsening of posturing to levels seen prior to surgical intervention following several programming visits. Patient 1 experienced an episode of worsening axial dystonia greater than levels seen preoperatively approximately 8 months after implantation, though it was unclear if this was related to worsening of his underlying progressive disease, as reprogramming following this occurrence provided substantial sustained benefit. These transient benefits with return to baseline necessitated frequent reprogramming, initially in clinic, but subsequently changes in parameters and stimulation contacts utilizing different groups through the patient programmer. If side effects were appreciated including orofacial dyskinesias or parasthesias, alternative contacts were trialed as well as consideration was made for bipolar stimulation to limit spread. Due to manufacturer limitations preventing utilization of bipolar stimulation on segmented contacts this was rarely utilized and instead alternative segmented contacts were trialed, as well as only constant voltage programming, as constant current programming is not currently allowed utilizing the combination of Sensight electrodes and the Activa RC generator. Cycling parameters were also trialed to limit neural plasticity (MacLean and Sanger, 2023), given concerns of acclimation, with patients noting to have different responses to different cycles, and requiring frequent adjustments and on/off cycling to achieve longer benefit as noted in their postoperative scores.

Given the wide range of frequencies reported in PPN stimulation (Ricciardi et al., 2019), once optimal contacts were identified stimulation was trialed at low (10–60 Hz), mid-range (60–95 Hz), and high (180–250 Hz) frequency. Patient 1 responded best to high frequency stimulation (200–250 Hz), while patients 2 and 3 responded best to low frequency stimulation (30–50 Hz.) All patients were noted to require only low voltage (< 1 V) stimulation in PPN for benefit, including up to 12 months post-implantation (Table 2).

3. Results

3.1. Benefits

Patients were assessed between 3 and 12 months postoperatively after having been stable on programming for at least 2 weeks to mitigate transient effects as reported. All subjects demonstrated significant improvement in the BFMDRS Motor score. Specifically, Patient 1 showed a 34.9% decrease, Patient 2 showed a 51.4% decrease, and Patient 3 showed an 80.0% decrease. Patients 2 and 3 also demonstrated improvement in the BADS, 39.3 and 35.3%, respectively. Patient 1 did not show any change in BADS between the pre- and post-operative time points. Average improvement on the BFMDRS was 55.4%, and average improvement on BADS was 24.9%. It is noted there is a wide range in the degree of improvement likely related to the heterogeneity of the patients' underlying conditions and symptoms. The lack of change seen in the BADS in patient 1 is likely related to the underlying severity of his dystonia and overflow component, which is not assessed in this scale, as well as its limitations in pediatric patients with other cooccurring tone concerns (Heringer et al., 2010). The response of all patients is shown in Table 3, as well as in Figure 2.

Additionally, component scores of the BFMDRS were separated into three categories to assess response in subgroups of relevant dystonic features: orofacial, axial, and extremities. The orofacial component is the sum of the scores for mouth, speech, and swallowing. The axial component is the sum of the scores for neck and trunk regions. The extremities component is the sum of scores for bilateral arms and legs. All patients demonstrated improvement in orofacial, axial, and extremities component scores. Patient 1 demonstrated 25.9% orofacial improvement, 44.4% axial improvement, and 34.8% improvement in extremities. Patient 2 demonstrated 27.8% orofacial improvement, 76.5% axial improvement, and 53.1% improvement in extremities. Patient 3 demonstrated 83.3% orofacial improvement, 83.3% axial improvement, and a 77.3% improvement in extremities. The average response in each category across all subjects was: 45.7% orofacial improvement, 68.1% axial improvement, and 55.1% improvement in extremities. Patients 2 and 3 experienced significant improvement in oral-pharyngeal dystonia evident on their scale scores. Patient 3 has experienced resolution of previous concerns for choking, as well as significant improvements in speech. Component scores for all patients are shown in Table 4, as well as in Figure 2.

TABLE 2 Stimulation parameters in PPN and GPi at time of post-operative assessment.

	Left PPN	Right PPN	Left GPi	Right GPi
Patient 1 (11 months post-operative)	Cycling with stimulation on for 1 min and off for 5 min	cycling with stimulation on for 1 min and off for 5 min	1b-2a-2c—case+	8-9c-10c—case+
	1c—case +	9c—case +	0.2 v	0.4 v
	0.2 v	0.2 v	90 μs	90 μs
	60 μs	60 μs	185 Hz	250 Hz
	250 Hz	250 Hz		
Patient 2 (3.5 months post-operative)	Cycling with stimulation on for 1 min and off for 5 min	Cycling with stimulation on for 1 min and off for 5 min	2—case+	9—case+
	2a—case+	10a—case+	2.5 v	2.5 v
	0.2 v	0.2 v	90 μs	90 μs
	60 μs	60 μs	190 Hz	190 Hz
	30 Hz	30 Hz		
Patient 3 (3.5 months post-operative)	Cycling with stimulation on for 0.1 s and off for 0.1 s	Cycling with stimulation on for 0.1 s and off for 0.1 s	01—case+	8—case+
	1c-2c—case+	9a—case+	3 v	3 v
	0.4 v	0.4 v	90 μs	60 μs
	50 μs	60 μs	185 Hz	185 Hz
	40 Hz	40 Hz		

TABLE 3 Clinical response to combined PPN and GPi stimulation.

	BFMDRS motor score		BADS	
	Pre-surgical	Post-surgical	Pre-surgical	Post-surgical
Patient 1	76	49.5	23	23
Patient 2	92.5	45	28	17
Patient 3	47.5	9.5	17	11

Patients and parents of patients were also asked if they thought deep brain stimulation improved their (or their child's) quality of life utilizing a Likert scale of "improved," "no change," or "worsening" quality of life concurrent with objective video scoring by the BADS and BFMDRS. Subjective quality of life improvements were noted by patient 1 and patient 3. Patient 2 could not answer due to cognitive/communicative limitations. The families of all three patients noted improvement in quality of life following DBS, with patient 2 family's particularly noting an improvement in sleep patterns including decreased wake after sleep onset.

3.2. Side effects

Similar to the effects commonly reported with DBS programming of various targets (Zarzycki and Domitrz, 2020), patients experienced parasthesias and worsening dystonic posturing with initial mapping and probing of the PPN stimulation contacts. In possible relation to the urge urinary incontinence previously reported in the Parkinson's disease cohort (Thevathasan et al., 2018), subject 2 experienced urinary retention of greater than 8 h during wakefulness with stimulation of specific contacts in PPN. This was replicated twice including with blinding of the patient and family utilizing previously set groups. Similar to the adult literature, we hypothesize this is likely related to the nearby pontine micturition center (Aviles-Olmos et al., 2011). Due to the cognitive limitations of the patient, it is impossible to characterize if retention is related to lack of urge.

None of the subjects experienced any perioperative or postoperative complications.

4. Discussion

Although pallidal DBS is well-established as the recommended target for Parkinson's disease and DYT1 dystonia, its utilization and targeting for other conditions has been mixed (Andrews et al., 2010). Variation in underlying etiology and clinical presentation of dystonia, particularly in many of the pediatric-onset dystonia conditions, further complicates the issue and increases the likelihood that a singular target is insufficient. Additionally, target choice is especially important depending on the physical distribution of dystonia. Pallidal and thalamic targets have shown promise in alleviating motor components of dystonia related to limbs and ambulation but have displayed inferior and often incomplete response to orofacial and axial presentations (Castelnau et al., 2005). This incomplete response has necessitated the exploration of alternative DBS targets in treatment of orofacial and axial dystonia.

Based on previous trials of PPN stimulation in PD patients (Thevathasan et al., 2018), we trialed PPN as a DBS target in three patients with childhood-onset dystonia. Despite the varying nature of etiologies underlying the three subjects presented in this report, commonalities in symptomatology included strong axial and orofacial dystonic components, motivating the choice to use PPN as an exploratory target in conjunction with pallidal DBS. All three subjects

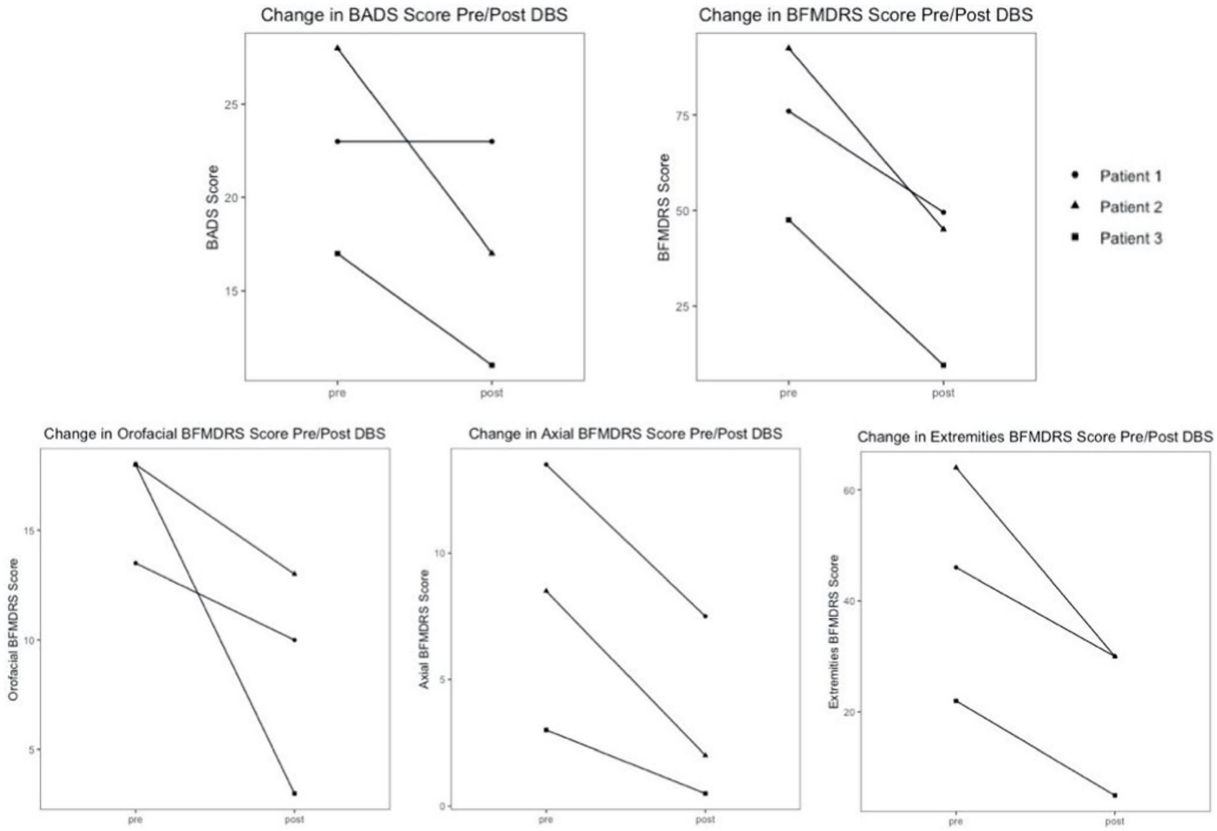

FIGURE 2
BADS and BFMDRS global/component motor scores pre- and post-operatively with combined PPN/GPi stimulation.

TABLE 4 Assessment of orofacial and axial response to combined PPN/GPi stimulation.

	Orofacial		Axial		Extremities	
	Pre-surgical	Post-surgical	Pre-surgical	Post-surgical	Pre-surgical	Post-surgical
Patient 1	13.5	10	13.5	7.5	46	30
Patient 2	18	13	8.5	2	64	30
Patient 3	18	3	3	0.5	22	5

showed marked improvements with combined pallidal and PPN stimulation, captured by the BADS and BFMDRS Motor Score. Orofacial, axial, and extremities BFMDRS component scores improved for all three patients. The improvement in both total and extremities component scores suggests that the predicted beneficial effects of pallidal DBS on dystonia in the extremities is preserved with combined PPN and GPi DBS. Additional subjective reports of improved quality of life and sleep present avenues for further examination including utilizing overnight polysomnography to further evaluate sleep changes as have been performed in the adult literature.

Figure 2 demonstrates that the range of percent improvements in motor scores across the cohort pre and post DBS is extremely wide, 45.1% difference between patient 1 and 3 in the BFMDRS, and 39.3% difference between patients 1 and 2 in the BADS scale. This highlights the amount of variation that is present in secondary dystonia, even when there are similarities in symptomatology, and emphasizes the importance of individualized programming post-operatively.

There are no reported cases of DBS in *MEPAN* hence we are unable to compare the patient's response to PPN to traditional stimulation within his condition. Limited literature in the GA1, pediatric population has shown mixed response to pallidal deep brain stimulation with a range of change in the BADS score of 0–18% (Shlobin et al., 2023), significantly lower than the 39.3% noted in patient 2 with combined PPN and Gpi DBS.

Of the three patients investigated in the report, maximal response was achieved in the third patient. Patient 3 was diagnosed with atypical PKAN, and achieved an 80.0% improvement in BFMDRS motor score, with 83.3% improvements in both orofacial and axial components, and 77.3% improvement in extremities. PKAN is known to respond to pallidal stimulation, as evidenced by a previous study of six subjects with both classic and atypical PKAN receiving bilateral pallidal stimulation. The study reported an average 65.1% improvement on the BFMDRS motor score in four subjects with classic PKAN, and average 85.0% improvement on the BFMDRS motor score in two subjects with atypical

PKAN (Castelnau et al., 2005). BFMDRS component scores were not reported, although suboptimal benefit in speech was noted. The improvement in global motor score with combined stimulation shown in this report is comparable to improvements seen with pallidal stimulation alone in PKAN. The 5% difference in benefit achieved in reported atypical PKAN scores could be explained by the difference in postoperative time point used, as scores reported for patient 3 in this study were measured 3 months postoperatively while scores reported in literature were measured at a minimum of 6 months postoperatively. Since the response to GPi stimulation is best observed longitudinally, further evaluation of combined PPN and GPi stimulation in the long-term is indicated. However, the degree of response in orofacial and axial areas shown in patient 3 highlights the positive clinical effects conferred by the addition of PPN stimulation.

The mechanisms of action of DBS on dystonia are not currently well understood (Lozano et al., 2019). GPi is considered to be the major output nucleus of the basal ganglia, exerting influence on both the thalamocortical loop via ventrolateral thalamus, and the brain stem—spinal cord via connections to PPN. In dystonia, there is evidence of signal abnormalities in the pallidum, suggesting that a possible mechanism of GPi DBS is that it alters or overrides these pathological signals without restoring normal function (Ostrem and Starr, 2008). Various human and non-human primate studies suggest that there is pathological underactivity of the PPN in both PD and dystonia, possibly related to cholinergic neural loss or overactivity of GABAergic projections from the GPi (Nowacki et al., 2019; Thevathasan and Moro, 2019; Su et al., 2022). A possible explanation for the motor benefits yielded by PPN DBS is that it partially ameliorates this depressed activity. Additionally, a key feature of development of dystonia is the imbalance between striatal dopamine and acetylcholine systems (Su et al., 2022). The PPN has extensive projections to dopaminergic neurons in the substantia nigra pars compacta, which could further explain the effect of PPN on motor function (Nowacki et al., 2019), as well as the presence of acetylcholine releasing neurons within PPN (Rye, 1997). The combined stimulation of GPi and PPN could play a role in stabilizing GABAergic, dopaminergic, and cholinergic interactions between basal ganglia, striatal, and PPN neurons. Although the exact mechanism of DBS, and the mechanisms of combined DBS, are unknown, it is possible that combined pallidal and PPN stimulation provide a coactivation effect that improves DBS outcomes for axial and orofacial symptoms. Further understanding of the mechanisms of DBS in single areas, as well as the interplay between DBS of multiple targets, could be very useful in establishing a methodology for optimal programming of PPN DBS, especially considering the transient effects of PPN DBS and variation in effective stimulation frequency reported in this cohort.

This cohort series is limited by its small and heterogenous patient population. Additionally, due to utilization of double bilateral stimulation in the subjects as part of typical clinical programming, we cannot adequately assess the results of PPN stimulation alone vs. in conjunction with pallidal stimulation. This assessment was particularly limited in clinical setting as subjects did not tolerate PPN stimulation being turned off, including when blinded to this change, with immediate worsening of axial dystonia. We also cannot ascertain if unilateral stimulation alone would have been sufficient for the clinical improvement appreciated by the patients and their families. Despite these limitations, this report describes the first known cases of DBS targeting of PPN in pediatric patients. While programming of PPN in combination with pallidal stimulation is complex and challenging, it may provide additional benefit in a subset of patient with axial and orofacial symptoms. Despite the difficulty associated with targeting PPN using standard techniques, all patients tolerated the procedure well, and no perioperative complications with DBS placement are reported. Patients displayed some sensitivity to stimulation frequencies and voltages, indicating that programming plays a strong role in success of the PPN target. However, all patients showed clinically significant improvements in BFMDRS scoring post-operatively, especially in scale subcategories associated with axial and orofacial features of dystonia. This suggests that PPN is a safe DBS target for pediatric secondary dystonia, and that co-stimulation of GPi and PPN may be an effective treatment paradigm for some components of dystonia that are insufficiently treated with GPi stimulation alone.

Data availability statement

The data presented in this study are available on request from the corresponding author, subject to patient consent to privacy. The data are not publicly available due to patient privacy.

Ethics statement

The studies involving humans were approved by Children's Hospital of Orange County Human Subjects Institutional Review Board Approval 200330, 13 July 2020 to 24 July 2024. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. HIPAA authorization for use of protected health information was obtained.

Author contributions

JM: Conceptualization, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. JN: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. JD: Writing – review & editing, Conceptualization. AZ: Writing – review & editing, Writing – original draft. JK: Conceptualization, Writing – review & editing, Methodology. ML: Conceptualization, Methodology, Writing – review & editing. JO: Conceptualization, Methodology, Writing – review & editing. TS: Conceptualization, Formal analysis, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A systematic review of health disparities research in deep brain stimulation surgery for Parkinson's disease

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Background: Deep brain stimulation (DBS) is the primary surgical intervention for Parkinson's disease (PD) patients with insufficient response to medication, significantly improving motor symptoms and quality of life. Despite FDA approval for over two decades, access to this therapy remains limited. This systematic review aims to evaluate the influence of gender, race/ethnicity, socioeconomic status, and age on health disparities associated with DBS for PD, providing an overview of current research in this field.

Methods: A systematic literature search was conducted in PubMed/MEDLINE, Embase, Web of Science and Cochrane databases from 1960 to September 12th, 2023, following Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Studies that examine the disparities in accessing DBS among patients with PD were included, comparing different demographic factors. Findings were synthesized and presented narratively to identify and understand DBS disparities.

Results: After screening for relevance, 25 studies published between 1960 and 2023 were included, with 16 studies meeting full-text review criteria. While reviewing the references of the 16 articles, two additional studies were included, bringing the total number of included studies to 18. Most studies originated from the United States (44%). The identified studies were categorized as identifying disparities, understanding disparities, or reducing disparities. The majority focused on identifying disparities (72%), while fewer studies delved into understanding the underlying factors (28%). No studies evaluated strategies for reducing disparities. The findings indicate that elderly, female, and Black people, as well as those from low socioeconomic backgrounds and developing countries face greater obstacles in accessing DBS for PD.

Conclusion: This study highlights factors contributing to disparities in DBS utilization for PD, including race, gender, and socioeconomic status. Public health policymakers, practitioners, and clinicians should recognize these inequalities and work toward reducing disparities, particularly among vulnerable populations.

KEYWORDS

deep brain stimulation, Parkinson's disease, health disparities, racial disparities, gender disparities, socioeconomic disparities, age disparities

Introduction

Reducing health disparities is a critical goal in healthcare, aiming to achieve equitable access and outcomes for all individuals, regardless of their demographic or socioeconomic background. In the context of deep brain stimulation (DBS) for Parkinson's disease (PD), addressing health disparities becomes particularly important due to the potential impact on patients' quality of life and disease management. Numerous randomized clinical trials (Perestelo-Pérez et al., 2014) have established the superiority of DBS over medication management in patients with PD. Moreover, considerable research has been dedicated to investigating DBS's mechanisms and advancements, particularly in white men (Lozano et al., 2019). However, there is a limited focus on expanding the accessibility of DBS to a broader patient population. Understanding how to make DBS more accessible is of utmost importance for future healthcare service planning, especially considering the projected rise in PD incidence within the next two decades to over 17 million globally (Dorsey et al., 2018).

Health disparities research has witnessed significant growth across various medical disciplines, consistently revealing associations between factors such as minority race, low socioeconomic status, and rural place of residence with poorer health outcomes (National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on Community-Based Solutions to Promote Health Equity in the United States, 2017). National initiatives are underway to address the high rates of preventable diseases among ethnic minorities, which are projected to incur an estimated cost of $50 billion annually to the healthcare system by 2050 (Waidmann, 2009). Implementing the Affordable Care Act (ACA) is a notable example, as it expanded coverage to over 20 million previously uninsured individuals and facilitated access to preventive services (Center on budget and policy priorities, 2019). However, while insurance expansion has demonstrated its ability to improve access to care, it only comprehensively addresses some of the patient-, provider-, and system-level factors contributing to health disparities. Therefore, further efforts are required to identify and address the underlying causes of these disparities beyond the scope of insurance expansion.

This study aims to systematically review the available evidence on DBS-related health disparities for PD populations. The primary focus is to review the research to date and describe findings on essential determinants of health inequity. These determinants include race, gender, socioeconomic status, and age, which have been examined within the literature on DBS. Additionally, we have also described potential solutions to address these disparities. Our study postulated a need for more research examining healthcare disparities across various domains in the availability of DBS for PD. Furthermore, we hypothesized that existing literature would focus on identifying disparities rather than developing strategies to mitigate and alleviate them.

Methods

Search strategy and study selection

A systematic review search was conducted by a medical librarian on September 12, 2023, in the following databases: Embase (via Elsevier), PubMed, Cochrane Library, and Web of Science. The searches followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al., 2009) and focused on disparities in access to DBS surgery for patients with PD.

A combination of database-specific subject headings and keywords were used in the search strategies. The concepts covered included (1) health disparities OR vulnerable populations: *("health disparity" [subject term] OR "vulnerable population" [subject term] OR "social determinants of health" [subject term] OR "disparit*" [keywords] OR "discriminat*" [keywords] OR "underrepresent*" [keywords] OR "underserved" [keywords] OR "marginalized" [keywords] OR inclusiv* [keywords])* AND (2) deep brain stimulation surgery: *("deep brain stimulator" [subject term] OR "brain depth stimulation" [subject term] OR "deep brain stimulation electrode" [subject term] OR "DBS" [keywords] OR "deep-brain" [keywords] OR "brain-depth" [keywords] NEAR/3 "surger*" [keywords] OR "stimulat*" [keywords] OR "procedur*" [keywords])* AND (3) Parkinson Disease: *("Parkinson Disease" [subject term] OR "PD" [keywords] OR "Parkinson*" [keywords] OR "hemiparkinsonism" [keywords])*. No date limits were applied. Specific study types were incorporated into the search strategies for PubMed, Embase, Cochrane Library, and Web of Science. Exact search strategies used for each database are included in the Supplementary Table S1.

Inclusion criteria required that articles were (1) peer-reviewed research studies, (2) included individuals diagnosed with PD, (3) studies specifically focused on DBS as a therapeutic intervention for PD, (4) incorporation of studies that investigate the availability, utilization, or accessibility of DBS; (5) studies that present findings on disparities, inequalities, or variations in the availability or accessibility of DBS for PD; (6) consideration of disparities arising from demographic factors, socioeconomic status, race/ethnicity, gender, age or other pertinent variables; (7) studies published in the English language.

Exclusion criteria included the following: (1) wrong patient population; (2) studies with wrong outcomes that do not provide data on racial, gender, socioeconomic and age disparities in DBS availability for PD; (3) studies with poor methodological quality or insufficient data to assess disparities or commentaries only. These exclusion criteria helped to focus articles selected on access disparities in DBS in patients with PD.

Risk of bias assessment

Using Joanna Briggs Institute's (JBI) (Moola et al., 2020) standardized critical appraisal instruments for observational studies, the quality of eligible studies was independently assessed by two investigators (KG and JM). This rigorous assessment aimed to ensure the internal validity of the review's findings and mitigate the potential influence of confounded or biased statistics. The selected studies were categorized into following study types: cross-sectional studies, retrospective cohort studies, case–control studies, and reviews. Specific checklists corresponding to each study type were utilized for assessment purposes. The evaluation checklists consisted of 8, 11, 10 and 11 questions for cross-sectional, retrospective cohort, case–control studies, and reviews, respectively (Moola et al., 2020). Responses to the checklist items were categorized as "Yes", "No," "Unclear," or "Not applicable." A score of "1" was assigned to "Yes" responses, while "0" was assigned to "No," "cannot be answered," or "not applicable" responses. The quality score for each study was calculated as a percentage and reported accordingly. The final score for each study was determined through consensus between the two evaluators (Table 1). In the event of any disagreements between the

TABLE 1 Risk of bias assessment.

Bias assessment of **Cross-sectional studies** using JBI critical appraisal checklist										
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Score	Score %
Chan et al. (2014)	Y	Y	Y	Y	Y	Y	Y	Y	8	100
Cramer et al. (2022)	Y	Y	Y	Y	Y	Y	Y	Y	8	100
Dorritie et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	8	100
Hamid et al. (2021)	Y	N	Y	N	U	N	NA	Y	3	37.5
Henriksen et al. (2020)	Y	Y	Y	Y	Y	Y	Y	Y	8	100
Jost et al. (2022)	Y	Y	Y	Y	Y	U	U	Y	6	75
Jourdain and Schechtmann (2014)	Y	Y	Y	Y	Y	NA	NA	Y	6	75
Meng et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	8	100
Setiawan et al. (2006)	Y	Y	Y	Y	N	N/A	Y	Y	6	75
Shpiner et al. (2019)	Y	Y	Y	Y	N	N/A	Y	Y	6	75
Watanabe et al. (2022)	Y	Y	Y	Y	U	U	Y	Y	6	75
Average score										83%

Y, Yes; N, No; U, Unclear; N/A, Not Applicable.
Q1: Were the criteria for inclusion in the sample clearly defined?
Q2: Were the study subjects and the setting described in detail?
Q3: Was the exposure measured in a valid and reliable way?
Q4: Were objective, standard criteria used for measurement of the condition?
Q5: Were confounding factors identified?
Q6: Were strategies to deal with confounding factors stated?
Q7: Were the outcomes measured in a valid and reliable way?
Q8: Was appropriate statistical analysis used?

Bias assessment of **Retrospective cohort studies** using JBI critical appraisal checklist												
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score	Score %
Chandran et al. (2014)	Y	Y	Y	N	N/A	Y	Y	Y	Y	N/A	Y	8	72.7
Deshpande et al. (2022)	Y	Y	Y	N	U	Y	Y	Y	U	U	Y	7	63.6
Skelton et al. (2023)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	10	90.9
Willis et al. (2014)	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	Y	8	72.7
Average score													75%

Y, Yes; N, No; U, Unclear; N/A, Not Applicable.
Q1: Were the two groups similar and recruited from the same population?
Q2: Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3: Was the exposure measured in a valid and reliable way?
Q4: Were confounding factors identified?
Q5: Were strategies to deal with confounding factors stated?
Q6: Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Q7: Were the outcomes measured in a valid and reliable way?
Q8: Was the follow up time reported and sufficient to be long enough for outcomes to occur?
Q9: Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
Q10: Were strategies to address incomplete follow up utilized?
Q11: Was appropriate statistical analysis used?

Bias assessment of **Case control studies** using JBI critical appraisal checklist												
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Score	Score %
Crispo et al. (2020)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	100
Average score												100%

Y, Yes; N, No; U, Unclear; N/A, Not Applicable.
Q1: Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
Q2: Were cases and controls matched appropriately?
Q3: Were the same criteria used for identification of cases and controls?
Q4: Was exposure measured in a standard, valid and reliable way?
Q5: Was exposure measured in the same way for cases and controls?
Q6: Were confounding factors identified?
Q7: Were strategies to deal with confounding factors stated?
Q8: Were outcomes assessed in a standard, valid and reliable way for cases and controls?
Q9: Was the exposure period of interest long enough to be meaningful?
Q10: Was appropriate statistical analysis used?

(Continued)

TABLE 1 (Continued)

Bias assessment of**Systematic Reviews** using JBI critical appraisal checklist													
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score	Score %
Hariz et al. (2011)	Y	Y	Y	N	Y	U	U	Y	N	Y	Y	7	63.6
Jamora and Miyasaki (2017)	Y	Y	Y	Y	U	U	U	NA	N	Y	Y	6	54.5
Average score													59.1%

Y, Yes; N, No; U, Unclear; N/A, Not Applicable.
Q1: Is the review question clearly and explicitly stated?
Q2: Were the inclusion criteria appropriate for the review question?
Q3: Was the search strategy appropriate?
Q4: Were the sources and resources used to search for studies adequate?
Q5: Were the criteria for appraising studies appropriate?
Q6: Was critical appraisal conducted by two or more reviewers independently?
Q7: Were there methods to minimize errors in data extraction?
Q8: Were the methods used to combine studies appropriate?
Q9: Was the likelihood of publication bias assessed?
Q10: Were recommendations for policy and/or practice supported by the reported data?
Q11: Were the specific directives for new research appropriate?

investigators, resolution was sought by engaging in discussions with another investigator (AAM).

Data extraction

Given the considerable diversity observed in study settings, participant characteristics, methodologies, exposure variables, and outcome measures across the included studies, a Meta-analysis was deemed inappropriate. Instead, a synthesis of findings was conducted by systematically extracting and organizing information from each manuscript. The results from the individual studies were presented and discussed using a narrative approach, complemented by the presentation of key findings in tabular formats. The conducted studies were systematically grouped into three primary categories, with the first category centered on the recognition and examination of disparities, the second delving into the exploration of the factors that underpin these disparities, and the third dedicated to the formulation and assessment of strategies aimed at mitigating these inequalities. This approach allowed for a comprehensive overview and interpretation of the collective evidence without relying on quantitative pooling methods.

Results

The process for manuscript selection is displayed in Figure 1. A total of 2,189 articles were identified in the literature review. Covidence removed 510 duplicate citations, leaving 1,679 unique references to be screened at the title/abstract stage. Two reviewers (KG and JM) independently conducted the initial review of the deduplicated titles and abstracts from the literature review for relevance, which led to the elimination of 1,654 citations (Figure 1). Subsequently, articles that met the initial inclusion criteria underwent a second review stage to identify the relevant 25 articles and evaluate study design quality. This process led to the exclusion of another 9 references, resulting in a set of 16 articles judged to be highly relevant and meeting the inclusion/exclusion criteria. While reviewing the references of the 16 articles, two additional studies were included, bringing the total number of included studies to 18. In cases where disagreements arose between the reviewers, a third reviewer (AAM) conducted an independent review to resolve them. The detailed process of study selection, including the reasons for excluding articles after the full-text review, is outlined in Figure 1.

The assessment of study quality in the included articles revealed that cross-sectional studies ($N = 11$) had an average quality score of 83%, retrospective cohort studies ($N = 4$) scored 75%, reviews ($N = 2$) scored 59.1% and case–control studies ($N = 1$) achieved a perfect score of 100%.

Regarding the categorization of the research, our analysis revealed that 13 studies (72%) were classified in the disparity detection category, focusing on identifying patterns and associations. In contrast, 5 studies (28%) were classified as the understanding disparities category, aiming to comprehend the underlying causes. However, no studies were identified in the reducing category, which entails developing interventions or strategies to mitigate the identified issues. Figure 2 in the infographic offers a concise overview of the paper's content.

Racial disparity

Our review revealed that the availability of DBS among Black individuals is lower (Chan et al., 2014; Willis et al., 2014; Cramer et al., 2022; Dorritie et al., 2023; Skelton et al., 2023). Table 2 provides details of the included studies. The following section presents a summary of studies categorized within the understanding phase of research, shedding light on factors contributing to the observed disparities.

One pioneering retrospective study investigated potential barriers to DBS access within the Black population (Chan et al., 2014). Analyzing a National inpatient sample (NIS) in the United States, 240,8302 PD discharges from 2002 to 2009 were examined, among which 18,312 discharges were associated with DBS. Notably, Black patients accounted for 4.7% of all PD discharges, but only 0.1% of DBS-related discharges. Utilizing the Hierarchical Logistic Regression Model, the authors identified Medicaid utilization as a predictor of

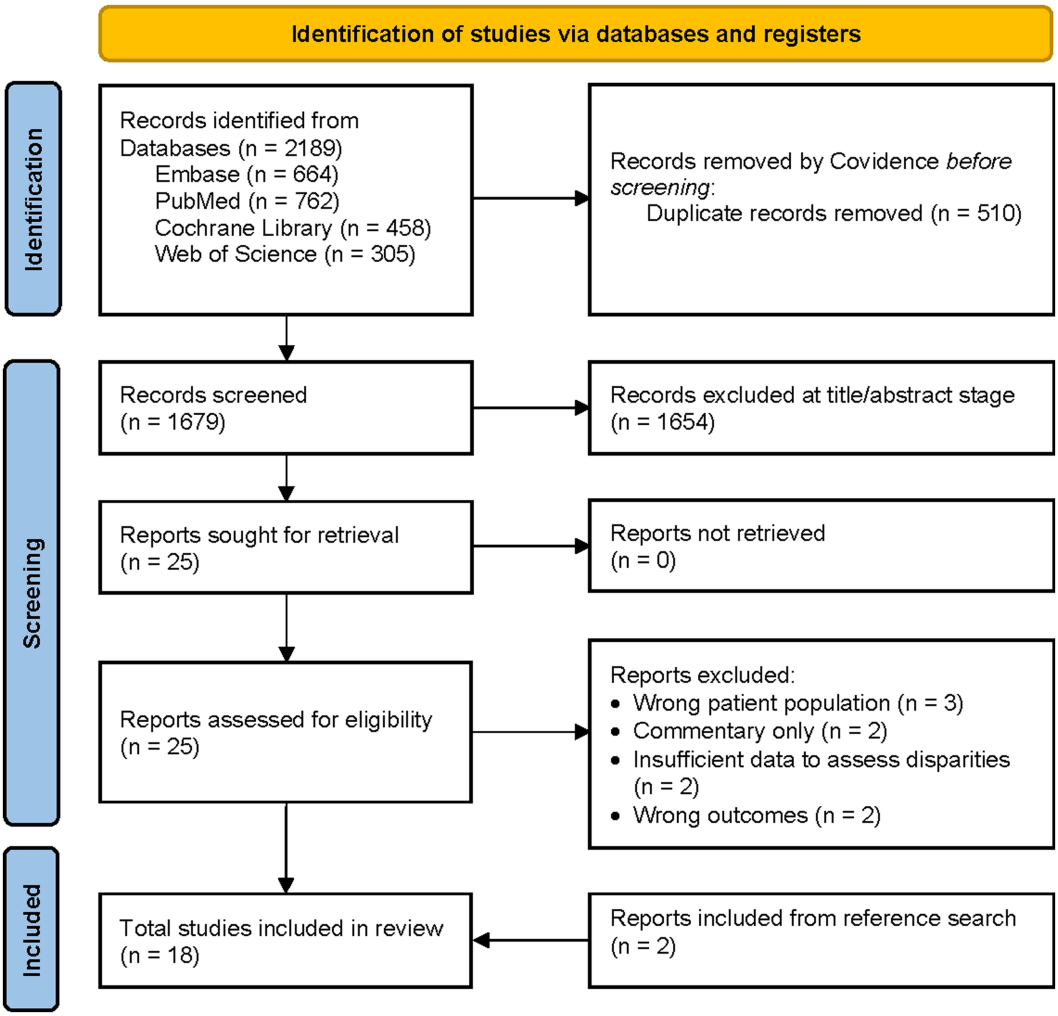

FIGURE 1
PRISMA flow diagram.

reduced DBS utilization in the Black population compared to those with private insurance or Medicare coverage. Similar results were found in a recent study that also queried the NIS database for United States hospitalizations from 2012 to 2018. It revealed that Black patients were less likely to receive DBS, primarily due to insurance and low income (Dorritie et al., 2023).

Other investigations aimed to assess whether racial disparities in DBS utilization for PD have improved over time (Cramer et al., 2022). One study utilized the NIS data spanning from 2002 to 2018. Despite observing an overall increase in the odds of DBS placement during the study period, the researchers discovered that Black patients were still five times less likely to undergo DBS than White patients.

Another study sought to investigate potential factors contributing to the racial treatment gap in DBS access during the preoperative surgical workup, with a specific focus on the experience of a single institution (Skelton et al., 2023). Through a retrospective analysis, this study examined all patients diagnosed with PD who underwent evaluation for DBS at Emory between 2016 and 2020. Despite the racial diversity observed in the metropolitan area served by the institution, DBS was underutilized in Black patients with PD. Importantly, this treatment gap was not found to be attributable to factors within the preoperative surgical selection process. The authors speculated that the discrepancy in DBS accessibility among PD patients of Black race arises during the clinical process preceding the evaluation for DBS candidacy.

Gender disparity

Our current review found a gender disparity (Hariz and Hariz, 2000; Setiawan et al., 2006; Willis et al., 2014; Shpiner et al., 2019; Cramer et al., 2022; Deshpande et al., 2022; Jost et al., 2022; Watanabe et al., 2022) and suggested that the proportion of male patients undergoing STN DBS appears to exceed the reported 1.48: 1 male-to-female ratio among patients with PD (Katz et al., 2011; Moisan et al., 2016; Shpiner et al., 2019). Three research studies sought to elucidate the factors underlying the observed gender disparity.

One retrospective study (Shpiner et al., 2019) analyzed data from a single center, investigating a cohort of 3,251 patients diagnosed with PD. Among this cohort, 207 individuals were referred for DBS surgery, with 100 ultimately undergoing the procedure. Of the 107 who did not have DBS, women were less inclined to undergo DBS surgery,

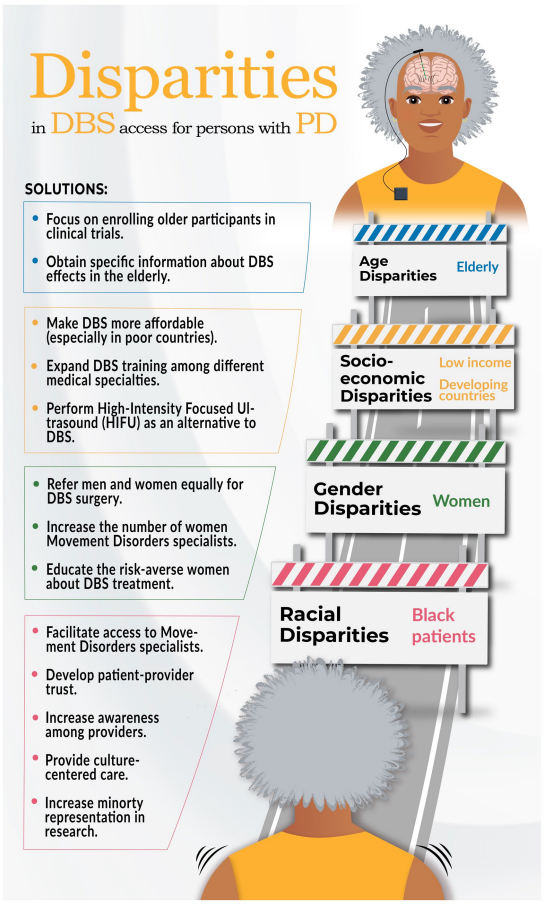

FIGURE 2
Infographic on health disparities research in DBS surgery for PD and potential solutions.

primarily due to their personal preference, while men were more prone to being lost to follow-up.

Deshpande and colleagues conducted a single-center, retrospective cohort study to examine the potential gender disparities in the time interval between the initial diagnosis of PD and the utilization of DBS therapy (Deshpande et al., 2022). The researchers analyzed gender differences in the median duration between the date of diagnosis, consultation for DBS, and the actual DBS surgery dates. The results of the study revealed no statistically significant differences between men and women in the interval from the diagnosis to DBS surgery for PD cases.

Gender disparities in referrals for DBS surgery among individuals with PD were comprehensively studied in a cross-sectional and longitudinal, prospective, observational, controlled, quasi-experimental, and international multicenter components (Jost et al., 2022). The findings revealed a significant underrepresentation of women with PD in the referral process compared to the general PD population, with a gender ratio of men to women of 2.1:1, higher than the ratio observed in PD diagnosis. The study identified various reasons for women not undergoing DBS surgery, despite positive indications during evaluations. These reasons included patients wishing for an additional period of reflection, patient preferences for further medical optimization, newly diagnosed or worsened preexisting comorbid diseases, language barriers, and undisclosed personal reasons. Additionally, general practitioners and neurologists referred fewer women than men for DBS evaluations, indicating a gender bias in referral patterns. The authors speculated that hospital medical staff might contribute to the observed gender disparities due to implicit or explicit bias since all surgical candidacy assessments were conducted in an inpatient care setting. As inpatient care setting allowed ample time to convey the rationale and clinical reasoning for DBS treatment when positive indication evaluations were present.

Socioeconomic and geographic disparities

Geographic factors, including limited availability of specialized healthcare facilities in specific regions, can influence disparities in the utilization of DBS. For instance, a review by Jamora and Miyasaki identified a scarcity of movement disorders specialists in the Philippines, with only 9 specialists serving a population of 100.98 million (Jamora and Miyasaki, 2017). Moreover, DBS services were solely accessible in the city of Manila. Similarly, in African countries, which are projected to surpass the combined population of North America, Europe, Latin America and the Caribbean, and Oceania by year 2050 (World Health Organization, 2017), DBS was only available in Egypt, Morocco, and South Africa, with occasional availability in Algeria and Tunisia (Hamid et al., 2021). However, the high cost of DBS due to lack of insurance rendered it unaffordable for most patients in these regions. Furthermore, a large-scale multicenter study utilized data from a national census spanning 74 Chinese centers (Meng et al., 2023) and similarly found that the eastern regions had significantly larger PD populations undergoing DBS compared to provinces in the western region. This discrepancy was attributed to the fact that provinces located in the eastern region demonstrated notably higher gross domestic products when compared to their counterparts in the western and northwestern regions (Meng et al., 2023).

In a survey conducted by Jourdian and Schechtmann involving neurosurgeons from 51 countries who had performed surgical procedures on 13,200 patients in 2009, it was observed that public healthcare systems often financed surgical procedures for PD making DBS more accessible (Jourdain and Schechtmann, 2014). Conversely, in both lower and upper-middle-income countries, patients frequently self-financed their surgeries and primarily opted for ablative surgeries rather than DBS.

Surprisingly, despite free public healthcare systems, health disparities in accessing DBS for PD persist. A study conducted in Denmark revealed the existence of barriers that result in unequal access to DBS based on factors such as age, gender, marital status, and socioeconomic status (Henriksen et al., 2020). Their findings indicated that PD patients who were male, below 70 years of age, had a partner, and possessed higher levels of education (indicative of higher socioeconomic status) were more likely to receive DBS than others. Similarly, a study conducted in Ontario, Canada examined 46,237 PD patients, among whom 543 underwent DBS surgery (Crispo et al., 2020). The Canadian study identified regional disparities, as patients residing in northern Ontario were more likely to receive DBS surgery than those in southern regions. Additionally, patients residing in neighborhoods with a higher concentration of visible minorities were less likely to receive DBS surgery than those in predominantly white neighborhoods. Furthermore, regular neurologist care and multiple PD medications were positively associated with the likelihood of DBS

TABLE 2 Summary of studies on health disparities research in DBS surgery for PD.

Study	Type of study	Study purpose/aim	Study sample	Exposure primary (secondary)	Testing phase	Main results % findings
Chan et al. (2014)	• Cross-sectional National Inpatient Sample • USA	To examine deep brain stimulation use in Parkinson disease to determine demographic, clinical, and socioeconomic variables that influence DBS use.	*N* = 2,408,302 African American *N* = 114,168 Other *N* = 2,294,134	Race (insurance status)	Detecting	African Americans accounted for only 4.7% of all PD discharges and 0.1% of DBS-related discharges.
Chandran et al. (2014)	• Cohort • Single-center • India	To investigate differences in gender and clinical characteristics in patients referred for DBS, and the outcomes when resources are limited.	*N* = 51 Female *N* = 19 Male *N* = 32	Gender	Detecting	Despite no gender difference in age of onset, duration, or severity of motor symptoms prior to DBS placement, women were on lower doses of dopaminergic medications. Women also had worse depression and emotional scores.
Cramer et al. (2022)	• Cross-sectional • National Inpatient Sample • USA	To determine whether racial and socioeconomic disparities in the use DBS for PD have improved.	*N* = 4,662,026 Black *N* = 255,284 Other *N* = 4,406,742	Race	Detecting	Despite an overall increase in the odds of DBS placement from 2002 to 2018, Black patients remained five times less likely to undergo DBS than White patients.
Crispo et al. (2020)	• Case control • Institute for Clinical Evaluative Services (ICES) datasets • Canada	To examine sociodemographic characteristics and health care utilization impacts on DBS surgery for PD.	*N* = 2,207 Northern Ontario *N* = 133 Southern Ontario *N* = 2059	Sociodemographic region	Detecting	Before controlling for medication use, patients in northern Ontario were more likely to receive DBS than patients in southern Ontario. Patients living in neighborhoods with more visible minorities had less access to DBS compared to patients in predominantly white neighborhoods.
Deshpande et al. (2022)	• Cohort • Single-center • USA	To assess whether a gender disparity exists from diagnosis to DBS surgery.	*N* = 53 Female *N* = 18 Male *N* = 35	Gender	Understanding	There was no gender difference in the timeline from diagnosis to DBS surgery.
Dorritie et al. (2023)	• Cross-sectional • National Inpatient Sample • USA	To identify racial and ethnic disparities in DBS utilization in those hospitalized for ET, PD, and dystonia.	*N* = 21,963 Black *N* = 1,469 Other *N* = 20,494	Race (Insurance Status, Socioeconomic Status, Sociodemographic Region)	Detecting	Between 2012–2018, Black patients with PD were 7 times less likely to receive DBS compared to White patients.
Hamid et al. (2021)	• Continent-wide Survey distributed to physicians specializing in PD across Africa	To investigate availability, affordability, and insurance coverage of PD therapies and services across Africa.	*N* = 28	Sociodemographic Region	Understanding	DBS was available in 5 of the 28 African countries represented.
Hariz et al. (2011)	• Systematic literature review	To evaluate the gender distribution of patients with PD who receive STN DBS.	*N* = 3,880 Female *N* = 1,435 Male *N* = 2,445	Gender (region)	Detecting	The proportion of male patients receiving DBS appears to exceed the reported male-to-female ratio among patients with PD.
Henriksen et al. (2020)	• Cross-sectional study • National Patient Register • Denmark	To investigate access to device-aided therapy for PD across Denmark.	*N* = 612	Gender	Detecting	Access to device-aided therapy for PD is unequally distributed across regions in Denmark.
Jamora and Miyasaki (2017)	• Pragmatic review • Philippines	To identify treatment gaps in the care of PD patients.	N/A	Socioeconomic status (region)	Detecting	There are only 3 neurosurgeons in the Philippines. DBS is only available in two medical centers in Manila. Lack of neurologist care and need for self-funding limit the access of DBS treatment.
Jost et al. (2022)	• Cross-sectional • Single-center • Germany/UK	To examine gender proportions from referral to DBS surgery, and differences in baseline and post-operative outcomes.	*N* = 316 Male *N* = 214 Female *N* = 102	Gender	Detecting	Although women had longer duration of disease and greater dyskinesia, they were underrepresented in DBS referrals.
Jourdain and Schechtmann (2014)	• Survey • Worldwide	To investigate the worldwide practice of DBS for PD.	*N* = 353	Socioeconomic Status	Detecting	Public health systems provide opportunity for surgical procedures in high-income countries, while lower income countries require financing by the individual resulting in more often ablative procedures.

(Continued)

TABLE 2 (Continued)

Study	Type of study	Study purpose/aim	Study sample	Exposure primary (secondary)	Testing phase	Main results % findings
Meng et al. (2023)	• Cross-sectional • Multi-center • China	To investigate utilization, surgical populations, centers, coverages, regional balance, and influential factors of DBS in PD.	*N* = 38,122	Sociodemographic Region	Understanding	More patients receive DBS surgery in provinces in the eastern and central regions of China with higher socioeconomic status and greater insurance availability.
Setiawan et al. (2006)	• Cross-sectional • Single-center • Canada	To determine whether gender proportions were respresented in DBS referrals, and identify reasons patients did not recieve DBS.	*N* = 91 Male *N* = 63 Female *N* = 28	Gender	Detecting	With equal amounts of male and female patients with movement disorders, just 31% of those referred for surgery were women.
Shpiner et al. (2019)	• Cross-sectional • Single-center • USA	To determine if a gender disparity exist in DBS surgery for PD, and the reasons at a single health system.	*N* = 3,251 Male *N* = 2013 Female *N* = 1,237	Gender	Understanding	Women were more likely to refuse DBS surgery due to personal decision.
Skelton et al. (2023)	• Cohort • Single-center • USA	To identify sources of racial disparity in DBS for PD.	*N* = 209 Black *N* = 10 Other *N* = 199	Race (Insurance Status)	Detecting	Disparity in access to DBS among Black PD patients occurs in the clinical process prior to evaluation for DBS candidacy (at or before the referral stage).
Watanabe et al. (2022)	• Cross-sectional • Single-center • USA	To characterize the PD population and disparities of DBS use in AA subgroups and NHPI patients.	*N* = 4,215 NHPI *N* = 409 Other *N* = 3,806	Race (Gender)	Understanding	There is an overrepresentation of males receiving DBS, most notably in the native Hawaiian or pacific islander cohort which 100% were male.
Willis et al. (2014)	• Cohort • Medicare research-identifiable files • USA	To identify sociodemographic, clinical, and physician/practice factors in DBS.	*N* = 665,765	Sociodemographic	Detecting	Within Medicare beneficiaries, Black patients, women, and those outside of the top quartile SES neighborhoods were less likely to receive DBS.

surgery, emphasizing the importance of access to specialists in reducing disparities related to access to DBS.

Age disparity

PD primarily affects the elderly, yet clinical trials investigating DBS often inadequately represent this demographic, and the use of DBS in elderly patients remains understudied (Krack et al., 2003; Deuschl et al., 2006). After reviewing the available literature, we found no studies addressing age disparities, which emphasizes the need for more research in this field. Additionally, Delong et al.'s study showed that older patients with PD (>75 years) selected for DBS surgery experienced similar 90-day complication risks as younger patients, suggesting that age alone should not be the sole factor for excluding candidates from DBS treatment (DeLong et al., 2014).

Discussion

Health disparities in DBS for PD need significantly more attention. While the benefits of DBS for PD have been extensively documented, there is still a lack of comprehensive understanding regarding the extent and nature of health disparities in DBS utilization across diverse populations. In contrast to our initial hypothesis, our analysis revealed that the majority of studies focused on identification of disparities, with only a limited number addressing understanding the factors underlying the disparities. These studies demonstrated that women, Black patients, individuals from low socioeconomic status backgrounds, and those residing in developing countries were particularly vulnerable to disparities in DBS access. The disparities remained unexplored among older patients despite PD primarily affecting the older population. As a result, our discussion will primarily center around the racial, gender and socioeconomic factors contributing to these disparities, shedding light on the complex interplay of various elements of inequity within the context of DBS utilization for PD.

Racial disparities

The findings in this comprehensive review confirm that DBS is often underutilized among Black patients and other racial minorities with PD. Moreover, the racial disparity in DBS utilization has remained relatively unchanged over the past decade (Cramer et al., 2022), with most data focusing on Black and White populations collected exclusively in the US, and there is no available data on other races. While most studies conducted thus far have focused on identifying the existence of this disparity, only a few have delved into the underlying causes and factors contributing to this phenomenon.

The findings of Skelton and colleagues showing a significant underutilization of DBS among Black patients with PD at an early stage, with a limited number of Black patients being referred for evaluation (Skelton et al., 2023) suggest the presence of potential unconscious or implicit bias, as well as other systemic factors contributing to the observed disparity (Wilson and Din, 2018). Consequently, there is a clear need for interventions to modify physician behavior and improve the referral and selection processes.

Moreover, it is essential to consider the role of marketing in exacerbating the upstream disparities, as Black patients are less likely to be exposed to direct-to-consumer marketing efforts than their white counterparts (Lee and Begley, 2010). Addressing the disparity in the referral system requires implementing various strategies, such as continuing education, computerized decision support systems, and reminders, as these strategies have shown effectiveness in modifying behavior (Mostofian et al., 2015). Incorporating these strategies into medical training and enhancing access to movement disorders specialists can alleviate the disparities in DBS utilization (Devine et al., 2012; Maina et al., 2018).

Disparities in surgical outcomes among racial groups can potentially contribute to the observed racial disparity using DBS. One notable factor contributing to these disparities is the long-standing mistrust and deep-rooted distrust that Black patients harbor toward the healthcare system, which can be traced back to historical events such as the well-known Tuskegee syphilis study (CDC, 1932). This pervasive mistrust and fear significantly impact Black patients' attitudes and behaviors, leading to greater hesitancy and reluctance to undergo DBS surgery (Scharff et al., 2010). This distrust underscores the critical importance of acknowledging and thoroughly studying the various factors that hinder access to care for racial minorities. However, several studies have reported no significant differences in surgical complications related to DBS for PD between Black and White patients (Fana et al., 2019; Skelton et al., 2023). Educating healthcare providers and raising awareness among Black patients about these comparable surgical outcomes is crucial for fostering equity in DBS utilization. Ensuring that both patients and healthcare professionals are well-informed can address some of the barriers that contribute to the observed racial disparities in DBS treatment.

Socioeconomic factors may significantly contribute to the observed disparities in DBS utilization among racial minorities. Research conducted by Chan and colleagues revealed that Black patients increased reliance on Medicaid predisposed them to the DBS disparity (Chan et al., 2014). Surprisingly, white patients utilizing Medicaid received significantly more DBS surgeries than Black patients using private insurance and Medicare, indicating that a distinct combination of Medicaid and race/ethnicity is responsible for the observed access disparity (Chan et al., 2014). Further investigations are warranted to comprehensively understand the relationship between socioeconomic factors, cultural factors, and Medicaid utilization in the context of DBS access (Eskandar et al., 2003; Katz et al., 2011; Dorritie et al., 2023). Exploring the complex interplay between these factors can provide valuable insights into the mechanisms underlying the DBS disparity among racial minorities and inform the development of targeted strategies to mitigate these disparities.

It is important to note that comorbidities do not appear to be the underlying factor contributing to the racial disparity in DBS utilization (Cramer et al., 2022). Black patients with PD tend to under-report motor symptoms and receive diagnoses later in their illness, often perceiving PD as a natural part of aging and thus being less inclined to seek treatment (Dahodwala et al., 2011). Furthermore, the underrepresentation of diverse ethnicities in the PD diagnosis criteria, primarily derived from analyses of Caucasian populations, may contribute to the observed disparity (Schneider et al., 2009). One potential approach to addressing this disparity is to increase the representation of racial minorities in the medical field, particularly in specialties such as movement disorders and neurosurgery. Patient-physician racial/ethnic concordance enhances communication and patient satisfaction (Saha et al., 1999), potentially facilitating Black patients' willingness to disclose their medical conditions to healthcare providers. Implementation of culture-centered care, providing trained language interpreters, incorporating faith-based resources, and offering incentives to manufacturers and medical providers that align with the racial distribution of the general population are some potential strategies to promote equity in healthcare for racial minorities (Ojukwu et al., 2020). Further research is necessary to investigate the role of comorbidities and surgical outcomes in contributing to the racial disparity in DBS utilization. Addressing these factors and providing culturally sensitive care are crucial steps toward reducing disparities in access to DBS for racial minority populations.

Gender disparities

This comprehensive review of the literature highlights disparities based on gender in the utilization of DBS for PD, which aligns with prior research examining disparities in access to invasive treatments for cardiac and gastrointestinal conditions (Hvelplund et al., 2010; Chibber and Baranchuk, 2020). Several studies have identified a notable gender disparity in the utilization of DBS for PD, with a significantly higher proportion of men undergoing the procedure than women and these studies have been conducted in various countries (Hariz et al., 2003, 2013; Mathkour et al., 2017; Deshpande et al., 2022). These findings emphasize the need for additional study regarding potential unconscious bias among healthcare providers, variations in the clinical indications for surgery based on gender, concerns specific to women regarding surgical complications, and gender-specific coping mechanisms for managing disease symptoms.

Referral bias due to gender has been identified as a contributing factor to the observed gender disparities in the utilization of DBS for individuals with PD (Jost et al., 2022). Specifically, women with PD are less likely to be referred for DBS evaluation by general practitioners and neurologists, leading to fewer women undergoing DBS surgery. This raises the question of whether the lack of diversity in the medical field plays a role in these disparities. Increasing the representation of women in movement disorders and neurosurgery specialties is one potential approach to address this disparity. Additionally, research on patient preferences for physician characteristics has shown that female patients prefer gender-concordant providers, highlighting the significance of promoting diverse representation within healthcare settings (García et al., 2003).

Differences in the clinical presentation and progression of PD have been observed between men and women, with women tending to experience longer disease duration, greater severity of dyskinesia, and more reduction in motor scores with medication (Haaxma et al., 2007; Shpiner et al., 2019). These variations in clinical phenotype may influence the decision to undergo DBS and contribute to the observed gender disparities. However, when it comes to clinical outcomes and responses to DBS, existing research suggests that men and women show comparable results in terms of quality of life, motor symptoms, medication needs, and motor outcomes (Chandran et al., 2014; Shpiner et al., 2019; Deshpande et al., 2022; Jost et al., 2022). These

findings suggest that nonclinical factors likely play a role in the observed gender gap in DBS utilization.

Nonclinical factors, such as patient self-selection and preferences, have been found to contribute to the gender disparities in DBS utilization. Female patients often cite personal preferences and a heightened fear of complications as reasons for not pursuing DBS (Hamberg and Hariz, 2014; Shpiner et al., 2019), despite the same complication rates between men and women. One possible explanation for this is related to risk-taking behavior, as studies in psychology have shown that men exhibit a higher propensity for risk-taking behavior (Rolison et al., 2014). Additionally, individual factors and follow-up patterns further contribute to the complex interplay between gender and the decision-making processes related to DBS utilization. For example, the caregiving dynamics for women with PD differ, as they are less likely to rely on a spouse as their primary caregiver, more inclined to employ paid caregivers, and frequently attend appointments independently (Dahodwala et al., 2018). Incorporating social work consults into their care plan and ensuring access to home healthcare services could offer valuable support in addressing these distinctive needs and challenges.

To address the gender disparities in DBS utilization, promoting awareness and education about DBS among women with PD is crucial. Providing accurate information can help address misconceptions or concerns and empower women to make informed decisions about their treatment options. The insights gained from the Parkinson Foundation Women and PD TALK PCORI project (Parkinson's Foundation, 2019) can be utilized to tackle DBS disparities by tailoring care approaches to address women's specific priorities, leading to improved treatment outcomes. Furthermore, this valuable information can guide researchers in studying gender-related factors, bridging knowledge gaps, and promoting equitable access to resources and support for women with PD. Future research should focus on exploring the decision-making processes of women with PD and investigating the clinical reasoning behind the referral patterns of general practitioners and neurologists. By understanding these factors more deeply, interventions can be developed to address and potentially mitigate the gender disparities in DBS utilization (Jost et al., 2022).

Socioeconomic disparities

Socioeconomic status encompasses factors such as income, access to transportation, social support, and the ability to take time off work for surgery and follow-up visits. Several studies conducted in various countries have identified socioeconomic status as a significant determinant of DBS utilization in patients with PD (Chandran et al., 2014; Henriksen et al., 2020; Cramer et al., 2022). These studies show that higher household incomes are associated with a greater likelihood of receiving DBS and achieving better functional outcomes compared to patients with lower socioeconomic status (Willis et al., 2014; Cramer et al., 2022). This may bias referrals toward patients with more significant financial resources, potentially leading to disparities in access to DBS and subsequent functional outcomes (Cramer et al., 2022).

In developed countries, Medicaid coverage, which is often associated with lower socioeconomic status, has been identified as a potential reason for lower rates of DBS surgeries among Black patients with PD (Chan et al., 2014). Conversely, in low-income and lower-middle-income countries, financial constraints, lack of insurance coverage, out-of-pocket expenditures, limited referrals, inadequate access to infrastructure, and the absence of multidisciplinary DBS teams have been identified as barriers to DBS utilization (Chandran et al., 2014; Jourdain and Schechtmann, 2014).

One potential solution to address the socioeconomic disparity in DBS utilization is to make DBS systems more affordable, particularly in developing countries. The high costs associated with DBS devices and procedures create barriers to access for individuals with limited financial resources. Lowering the prices of DBS systems would enhance accessibility for individuals from lower socioeconomic backgrounds (Zhang et al., 2020). For policymakers, government initiatives similar to Imran Khan's health insurance plan ("Sehat Sahulat program") that aims to provide health insurance coverage to low-income households can provide access to medical services at partner hospitals and healthcare facilities without incurring out-of-pocket expenses. This alleviates the financial burden on poor individuals seeking medical treatment in Pakistan could be implemented to improve access to DBS for individuals from lower socioeconomic backgrounds (Barber and Shahza, 2022).

Furthermore, alternative technologies such as high-intensity focused ultrasound (HiFU) may offer a potential solution (Krishna et al., 2023), as the expenses and post-surgical care associated with HiFU are less than DBS. Additionally, exploring the feasibility of performing HiFU by movement disorders-trained neurologists and neuroradiologists could expand access to this latest technology to provide surgical therapies for individuals in developing countries without neurosurgeons.

Surprisingly, despite having free public healthcare systems in developed countries like Denmark and Canada, disparities in the availability of DBS for PD still exist (Crispo et al., 2020; Henriksen et al., 2020). Regional variations in the distribution of neurologists and neurosurgeons are considered significant barriers to accessing DBS treatment. Referral patterns and disparities in the availability of movement disorders specialists and neurosurgeons across different regions are potential factors contributing to the limited availability of DBS for PD patients. Thus, it is crucial to take measures to increase the number of neurosurgeons and movement disorders-trained neurologists, especially in regions where specialist care is less accessible, in order to mitigate this disparity.

Limitations

This systematic review is based on studies with limitations that must be acknowledged. Most studies are derived from single-center experiences (Chandran et al., 2014; Shpiner et al., 2019; Deshpande et al., 2022; Watanabe et al., 2022; Skelton et al., 2023), capturing only the final stages of the extensive clinical pathway for DBS surgeries and may restrict the generalizability of the findings. The small sample sizes in some studies limit the statistical power of the primary outcomes (Shpiner et al., 2019; Deshpande et al., 2022; Watanabe et al., 2022; Skelton et al., 2023). Additionally, using the NIS dataset (Chan et al., 2014; Willis et al., 2014; Cramer et al., 2022; Dorritie et al., 2023), which is retrospective, introduces limitations related to coding accuracy and data completeness. Furthermore, the cross-sectional study designs employed in several studies hinder the systematic assessment of the reasons behind DBS disparities. Moreover, it is important to note that highly selected patients were

included in certain studies for good surgical outcomes, which may not be ideal for assessing gender differences in resource-poor countries (Chandran et al., 2014). Furthermore, surveys sent to societies to collect data on low and middle-income countries may have missed surgeons who are not society members or do not publish articles, potentially impacting the representation of the sample (Jourdain and Schechtmann, 2014).

Future studies should address these limitations by incorporating longitudinal designs to assess long-term outcomes, including the durability of benefits, disparities in follow-up care, and patient-reported outcomes such as quality of life and functional outcomes. Additionally, qualitative research should be conducted to gain insights into the experiences, perspectives, and decision-making processes of individuals from diverse populations, uncovering contextual factors, cultural beliefs, and social determinants that contribute to disparities and informing tailored interventions.

Conclusion

In summary, this study identified a range of factors that contribute to disparities in the utilization of DBS for PD, encompassing racial, gender, and socioeconomic disparities, as well as considerations related to financial constraints, geographic factors, education level, and healthcare-seeking behavior. Future research must acknowledge and address the limitations of existing studies, explore the intersectionality of these factors, and develop potential strategies to enhance equity in DBS therapy for individuals with PD. Efforts should be directed toward improving physician behavior, mitigating marketing disparities, promoting cultural sensitivity in healthcare delivery, and investigating the interplay between socioeconomic factors and healthcare utilization. By adopting a comprehensive approach, healthcare systems can strive to eliminate disparities and enhance the overall surgical management of PD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

AM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. KG: Data curation, Formal analysis, Methodology, Writing – review & editing. JM: Data curation, Formal analysis, Methodology, Writing – review & editing. RB: Methodology, Writing – original draft, Supervision. MF: Supervision, Writing – review & editing. CC: Supervision, Visualization, Writing – review & editing. SM: Supervision, Writing – review & editing. AA: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1269401/full#supplementary-material

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Deep brain stimulation for essential tremor versus essential tremor plus: should we target the same spot in the thalamus?

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Background: Although ET is a phenomenologically heterogeneous condition, thalamic DBS appears to be equally effective across subtypes. We hypothesized stimulation sites optimized for individuals with essential tremor (ET) would differ from individuals with essential tremor plus syndrome (ET-plus). We examined group differences in optimal stimulation sites within the ventral thalamus and their overlap of with relevant white matter tracts. By capturing these differences, we sought to determine whether ET subtypes are associated with anatomically distinct neural pathways.

Methods: A retrospective chart review was conducted on ET patients undergoing VIM DBS at MUSC between 01/2012 and 02/2022. Clinical, demographic, neuroimaging, and DBS stimulation parameter data were collected. Clinical characteristics and pre-DBS videos were reviewed to classify ET and ET-plus cohorts. Patients in ET-plus cohorts were further divided into ET with dystonia, ET with ataxia, and ET with others. DBS leads were reconstructed using Lead-DBS[1] and the volume of tissue activated (VTA) overlap was performed using normative connectomes. Tremor improvement was measured by reduction in a subscore of tremor rating scale (TRS) post-DBS lateralized to the more affected limb.

Results: Sixty-eight ET patients were enrolled after initial screening, of these 10 ET and 24 ET-plus patients were included in the final analyses. ET group had an earlier age at onset ($p = 0.185$) and underwent surgery at a younger age ($p = 0.096$). Both groups achieved effective tremor control. No significant differences were found in lead placement or VTA overlap within ventral thalamus. The VTA center of gravity (COG) in the ET-plus cohort was located dorsal to that of the ET cohort. No significant differences were found in VTA overlap with the dentato-rubral-thalamic (DRTT) tracts or the ansa lenticularis. Dystonia was more prevalent than ataxia in the ET-plus subgroups ($n = 18$ and $n = 5$, respectively). ET-plus with dystonia subgroup had a more medial COG compared to ET-plus with ataxia.

Conclusion: VIM DBS therapy is efficacious in patients with ET and ET-plus. There were no significant differences in optimal stimulation site or VTA overlap with white-matter tracts between ET, ET-plus and ET-plus subgroups.

KEYWORDS

essential tremor, essential tremor plus, deep brain stimulation, DBS target, VIM

1 https://www.lead-dbs.org

Introduction

Essential tremor (ET) is one of the most common movement disorders, affecting up to 1% of the world population, and its prevalence increases up to 4–5% in the elderly population (Louis and Ferreira, 2010; Clark and Louis, 2018; Shanker, 2019). Symptoms of ET often emerge in a bimodal distribution across age groups, affecting people in their second to third decades or after the fifth or sixth decades of life (Louis and Ferreira, 2010; Clark and Louis, 2018; Haubenberger and Hallett, 2018). ET is characterized by upper limb action and/or postural tremor and can affect areas such as the head, voice, and lower limbs. ET is typically inherited in an autosomal dominant fashion with reduced penetrance (Bhatia et al., 2018; Clark and Louis, 2018; Haubenberger and Hallett, 2018). The pathophysiology of ET remains incompletely understood but there is increasing neuroimaging and postmortem evidence of cerebellar pathology (Kuo et al., 2011; Bhalsing et al., 2013; Gionco et al., 2021; Holtbernd and Shah, 2021; Pan and Kuo, 2022). Specifically, the cerebello-thalamo-cortical loop plays a major role in ET tremorgenesis (Lenka et al., 2017; Nicoletti et al., 2020).

In 2018, the Tremor Task Force from the Movement Disorders Society (MDS) revised the consensus statement for tremor classification and introduced the diagnosis of Essential tremor plus (ET-plus). ET-plus is defined as "tremor with characteristics of ET and additional neurologic signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis" (Bhatia et al., 2018). The updated criteria emphasized the heterogeneity of ET syndrome, and the designation of ET-plus aimed to create a more refined patient selection in clinical research.

Propranolol and primidone are the most common first line treatments and may achieve up to 70% tremor reduction when used in combination (Koller and Royse, 1986; Ferreira et al., 2019). However, pharmacological treatment of ET and ET-plus is often inadequate and limited by undesirable side effects. Prior literature reported up to 50% of patients discontinuing medical therapy due to intolerance (Louis et al., 2010). Deep brain stimulation (DBS) has been the mainstay treatment for medically refractory tremor since its initial approval in 1997 (Iorio-Morin et al., 2020; Wong et al., 2020). Stimulation to ventralis intermedius nucleus (VIM) of the thalamus has demonstrated excellent efficacy in the treatment of medically refractory tremor, achieving up to 66–80% tremor reduction with sustained long term efficacy (Zhang et al., 2010; Dallapiazza et al., 2019; Paschen et al., 2019). Several targets have been explored for optimal tremor reduction including the posterior subthalamic area (PSA) and zona inserta (ZI) (Wong et al., 2020; Chandra et al., 2022). VIM remains the most common target as it provides better long-term efficacy, and stimulation to deeper targets may result in higher rates of stimulation induced ataxia and dysarthria due to involvement of the cerebellothalmic tracts (Iorio-Morin et al., 2020; Wong et al., 2020; Kremer et al., 2021; Chandra et al., 2022). Stimulation to the dentato-rubral-thalamic tracts (DRTT) with projected connections to the primary motor and supplementary motor cortices have been implicated to produce the most efficacy in tremor reduction (Iorio-Morin et al., 2020; Wong et al., 2020; Middlebrooks et al., 2021; Chandra et al., 2022). The DRTT connects the cerebellum to the thalamus with receiving fibers primarily in the VIM, and consists of both decussating (DRTT) and non-decussating (nDRTT) fibers (Gallay et al., 2008). Adjacent stimulation to the pallidothalamic tracts (ansa lenticularis and fasciculus lenticularis), which originate from the globus pallidus interna (GPi) with implications in the treatment of dystonia, has also demonstrated tremor efficacy (Gallay et al., 2008; Iorio-Morin et al., 2020; Horisawa et al., 2021).

Two recent studies have demonstrated similar efficacy in treatment of ET and ET-plus with VIM DBS (Steffen et al., 2020; Gilmour et al., 2021), but whether ET and ET-plus represent distinct clinical entities with varying underlying pathophysiology remains unexplored. We hypothesized that the effective stimulation site within the ventral thalamus may differ between ET and ET-plus subtypes. We aimed to focus specifically on two phenomenologically distinct ET-plus subtypes: ET-plus with dystonia and ET-plus with ataxia. We also hypothesized that the volume of tissue activated (VTA) overlaps with adjacent white matter tracts of ET subtypes would also differ. The pathophysiology of dystonia is hypothesized to involve both the cerebello-thalamo-cortical and the basal ganglia-thalamo-cortical networks. A recent study by Tsuboi et al. demonstrated slightly different functional and structural connectivity between dystonic and essential tremor (Middlebrooks et al., 2021). Animal and small cerebellar DBS studies have demonstrated aberrant hyperexcitability of the deep cerebellar nuclei as the potential culprit for symptoms of ataxia and kinetic tremor (Tai and Tseng, 2022). By capturing differences in tract engagement of VTA overlap to the optimal stimulation site in ET subtypes, we sought to determine whether these subtypes are pathophysiologically distinct from ET.

Materials and methods

We performed a retrospective chart and video review of all patients who underwent VIM DBS for ET and ET-plus at the Medical University of South Carolina between 01/2012 and 02/2022. ET was defined based on the tremor classification as "isolated tremor syndrome of bilateral upper limb action tremor, at least 3 years duration, with or without tremor in other locations (e.g., head, voice or lower limbs), and the absence of other neurological signs, such as dystonia, ataxia or parkinsonism" (Bhatia et al., 2018). ET-plus was defined as "tremor with the characteristics of ET and additional neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurological signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis" (Bhatia et al., 2018). Patients in the ET-plus cohort were further divided into ET-plus with dystonia, ET-plus with ataxia, and ET-plus with other based on characteristics observed in pre-operative videos. Inclusion criteria were: (i) clinical diagnosis of ET or ET-plus at the time of DBS implantation; (ii) DBS insertion in the VIM nucleus of the thalamus; (iii) pre-operative video available for review, (iv) preoperative brain MRI and postoperative CT data available. Exclusion criteria included were: (i) missing stimulation parameters; (ii) lack of efficacy data; (iii) suboptimal quality to preoperative MRI or postoperative CT images; (iv) significant surgical complications resulting in the removal of device or permanent neurologic deficits; and (v) concomitant comorbidities that would potentially confound the delineation of diagnosis or outcome measure (i.e., functional neurological disorder, history of CNS infection or traumatic brain injury).

Baseline clinical characteristics collected included: gender, race, ethnicity, handedness, age at onset of ET or ET-plus, more effected limb, age at surgery, family history of tremor, tremor characteristics (body distribution, activation conditions, symmetry), previous treatments, significant comorbidities, additional neurological signs of uncertain significance (e.g., dystonia, rigidity, bradykinesia, myoclonus, mild cognitive impairment identified during presurgical neuropsychologic evaluation, and/or impaired tandem gait).

Tremor characteristics to appropriately classify patients as having ET or ET-plus were extracted independently from pre-operative videos by one movement disorders specialist (CHY), with supplementation from paper charts for aspects of the examination not filmed (e.g., mild cognitive impairment, subtle abnormal posturing and/or irregular head tremor, impaired tandem gait, and/or subtle limb ataxia).

Tremor severity was evaluated using the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) motor scores (items 1–14) where higher scores indicated worse tremor. The primary outcome measure was a reduction in the pre- to post-operative tremor subscores, lateralized to the more affected limb before DBS implantation (Items 1–5, 7–8 for the right hand or items 1–4, 6–7, and 9 for the left hand).

Standard perioperative procedures

Prior to implantation, DBS candidacy was determined by a multidisciplinary team including movement disorders neurologists, neurosurgeons, neuropsychologists and speech and language pathologists. Preoperatively, a standard stereotactic targeting MRI was performed on a 3 T Siemens scanner (Siemens Healthineers AG), which included a high-resolution T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence optimized for differentiation of gray and white matter. The VIM was targeted using standard AC-PC coordinates (x = 11.5 lateral + half of the width of the third ventricle, y = anterior to posterior commissure (PC) by 20% of anterior commissure (AC) to posterior commissure line length, and z = along AC-PC line all measured in millimeters). DBS leads (Medtronic 3,389, Abbott 6,172, or Boston Scientific Vercise) were implanted under local anesthesia with additional guidance obtained with intraoperative microelectrode recordings and macrostimulation testing. We aimed to place the distal contact at the ventral border of the VIM. The latest available pulse generators were implanted. Three to four weeks after implantation, patients underwent postoperative CT scans and a monopolar review to evaluate the initial tremor-suppressing effects and adverse effects of each contact. A postoperative CT was obtained on Siemens helical CT scanner (Siemens Healthineers AG) with an in-plane resolution of 0.5 × 0.5 mm and slice thickness of 1 mm. Following monopolar review, patients had regular follow up visits to optimize their DBS settings. Clinical follow up period was defined by months after initial programming session with monopolar review.

DBS electrode localization

Lead localization was performed using Lead-DBS software (V2.6). Raw pre-operative MRI scans and post-operative CT scans were converted to NIFTI file formats using dcm2niix (Li et al., 2016). Post-operative CT scans were then co-registered to either a T1 or T2 pre-operative scan (depending on acquisition quality and availability) using a two-stage linear registration as implemented in Advanced Normalization Tools (Avants et al., 2008).[2] Other pre-operative MRI scans (e.g., PD, FGAITR, FLAIR) were co-registered with the T1 or T2 scan using SPM12.[3] Normalization of pre-operative and post-operative images to the MNI_ICBM_2009b_NLIN_ASYM template space was performed using the FNIRT approach as implemented in the FMRIB Software Library.[4] Image co-registration and normalization quality was manually reviewed. In the case of poorly co-registered images, volume registrations were redone using an alternative approach to maximize registration quality. DBS electrode localizations were corrected for brainshift in postoperative acquisitions by applying a refined affine transform calculated between pre- and postoperative acquisitions that were restricted to a subcortical area of interest as implemented in the brainshift-correction module of Lead-DBS software (see text footnote 1). DBS-Electrodes were manually localized based on post-operative acquisitions using a tool specifically designed for this task. 3D visualization of data was performed using the DISTAL atlas. Volume of tissue activated (VTA) were created by using stable, clinically programmed stimulation parameters determined during outpatient programming visits. VTAs were estimated in patient space using the SimBio/FieldTrip model as implemented in Lead-DBS and normalized into the MNI template space for further analyses (Horn et al., 2017). VTAs which were estimated in the right hemisphere were binarized and flipped to the left hemisphere to create VTA overlap maps in MNI space. Overlap maps were calculated by taking the sum of the binarized VTAs. Each lead was treated as an independent data point, with a total of 12 leads and VTAs reconstructed in the ET group and a total of 31 leads and VTAs reconstructed in the ET-plus group.

VTA center of gravity and fiber pathway analysis

Center of gravity analysis

To summarize differences in the anatomical location of VTA's within the ET and ET-plus groups, the center of gravity (COG) coordinates of the VTAs were calculated using FSL. The COG coordinate is the average location of VTA coordinates, weighted by the number of participants with VTAs at a given coordinate.

Fiber pathway analysis

To determine group differences in fiber activation between groups the overlap between VTAs and normative fiber pathways were calculated for each patient. The dentato-rubral-thalamic tract (DRTT), non-decussating dentato-rubral-thalamic tract (nDRTT) and ansa lenticularis fiber pathways were defined using a previously published diffusion tractography provided as an atlas in Lead-DBS (Middlebrooks et al., 2020). Two-sample t-tests were used to compare the number of overlapping voxels in the ET vs. the ET-plus group and considered significant if $p < 0.05$.

2 http://stnava.github.io/ANTs/
3 http://www.fil.ion.ucl.ac.uk/spm/software/
4 https://fsl.fmrib.ox.ac.uk/

TABLE 1 Baseline characteristics and DBS outcome.

	ET	ET-Plus	*P*
N	10	24	
Age at symptom onset, years	34.20 ± 19.85	40.79 ± 18.99	0.185
Age at DBS surgery, years	68.1 ± 7.40	71.5 ± 5.76	0.096
Gender (%Female)	30%	46%	
Race (%White)	100%	83%	
Family history of tremor (%Yes)	70%	71%	
Average follow up length, months	46.90 ± 28.12	31.58 ± 20.77	**0.044**
Baseline TRS, total	53.3 ± 8.60	53.4 ± 17	0.496
TRS unilateral pre-DBS (Items 1–5, 7–8 for right hand or items 1–4, 7 and 9 for left hand)	9.00 ± 9.73	10.09 ± 4.63	0.450
TRS unilateral post-DBS (Items 1–5, 7–8 for right hand or items 1–4, 6–7 and 9 for left hand)	(*N* = 8) 0.375 ± 0.52	(*N* = 16) 2.50 ± 1.67	**0.001**
TRS follow up period, months	(*N* = 8) 11.89 ± 6.41	(*N* = 16) 11.81 ± 9.28	0.491
TRS reduction, average	(*N* = 8) 82%	(*N* = 16) 70%	0.154

Data represented as mean ± standard deviation. Statistical analysis was performed using independent *t*-test. $p < 0.05$ is considered significant and shown in bold.

Statistical analysis of demographics and clinical data

Statistical analyses were performed using R (R version 4.2.2). Differences between groups at baseline in demographics and clinical data were assessed using one-way ANOVA. A *p*-value of less than 0.05 was considered significant.

Results

Sixty-eight ET patients who underwent VIM DBS at MUSC between 1/2012 to 2/2022 were included after initial screening with appropriate pre-operative MRI and post-operative CT imaging data. Thirty-four of these patients were excluded. Of the 34 patients included, 10 patients (29%) were characterized as ET, and 24 patients (71%) were ET-plus. Of note, 21 patients (87.5%) were re-classified as from ET to ET-plus. About 40% ($n = 4$) of the ET cohort and 38% ($n = 9$) of the ET-plus cohort underwent unilateral VIM DBS. The baseline demographics and clinical data of ET and ET-plus cohorts are summarized in Table 1. Within the ET-plus cohort, 18 patients were subcategorized as ET-plus with dystonia (75%), 5 patients as ET-plus with ataxia (21%), and 1 patient characterized as ET with other (parkinsonism) (4%). The individual data are provided in Supplementary Table S1.

ET patients had younger mean age at onset (age 34 for ET, and age 41 for ET-plus, $p = 0.185$) and underwent DBS surgery at a younger age (age 68 for ET and age 72 for ET-plus, $p = 0.096$). They had a significantly longer average length at follow up (47 months for ET and 32 months for ET-plus, $p = 0.044$). There was no significant difference between baseline tremor severity as measured by pre-DBS total TRS or unilateral TRS lateralized to the more affected limb. The ET cohort has a significantly lower post-DBS unilateral TRS lateralized to the more affected limb ($p = 0.001$). VIM DBS stimulation improved the contralateral TRS tremor sub scores for both ET and ET-plus cohorts [Table 1; average 82 and 70% for ET ($n = 8$) and ET-plus ($n = 16$) respectively, $p = 0.154$]. Pre- and post-DBS TRS scores were obtained approximately within 12 months for both ET and ET-plus cohorts. Additional characteristics including short term (1–2 years post-operatively) and final stimulation parameters are included in Supplementary Table S1.

Volume of tissue activated analysis

DBS electrode trajectories were recreated based on active contacts. Comparisons of ET and ET-plus trajectories in relation to thalamic nuclei and relevant white matter tracts are shown in Figure 1. DBS electrodes were primarily located at the VIM and ventralis oralis posterior (VOp) borders and were in close proximity to DRTT, nDRTT, and ansa lenticularis. The volume of tissue activated (VTA) for clinically optimized DBS electrodes for ET and ET-plus cohorts were created in Lead DBS as a heat map (Figure 2). The optimal stimulation region for ET and ET-plus correlated to the same region as represented in the VTA heat map. Figure 3 demonstrates the relative location of ET and ET-plus heatmap to adjacent relevant white matter tracts including DRTT, nDRTT and ansa lenticularis. For each group, a center of gravity (COG) analysis was also carried out. The COG for optimal stimulation for ET was located at MNI −13.8, −15.1, and −0.1 in the ventral VIM region, while the optimal stimulation for ET-plus was located at MNI −13.6, −15.6, and +1.3. The COG for ET-plus cohort was slightly more dorsal within the ventral VIM compared to ET cohort (Figure 4A). No significant group differences were found in VTA overlap with the DRTT ($t = 0.375$, df = 41, $p = 0.713$), nDRTT ($t = -1.173$, df = 41, $p = 0.247$) or the ansa lenticularis ($t = 1.675$, df = 41, $p = 0.102$) as shown in Figures 3, 4B. Additionally, overall VTA size did not differ between groups ($t = -1.416$, df = 41, $p = 0.164$).

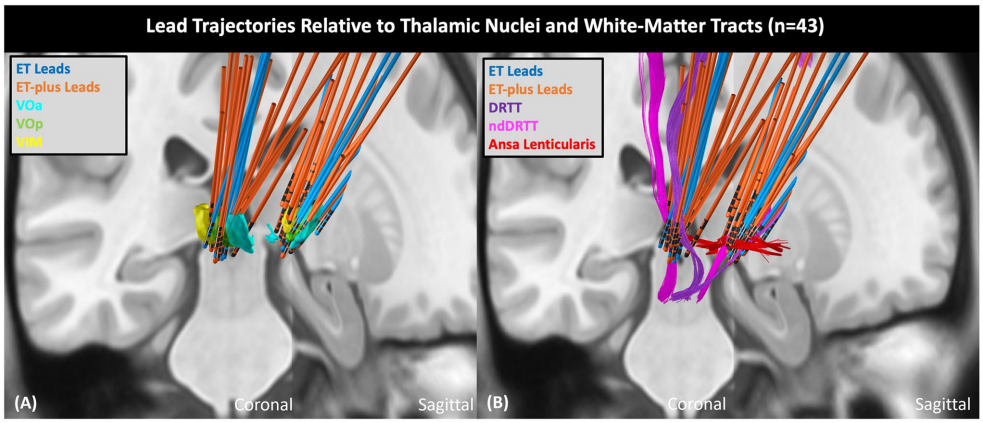

FIGURE 1
ET and ET-plus lead trajectories relative to thalamic nuclei and white matter tracts. **(A)** Shows DBS lead trajectories relative to thalamic nuclei in coronal (left) plane and sagittal (right) plane. **(B)** Shows DBS lead trajectories relative to adjacent white matter tracts. VOa, ventralis oralis anterior nucleus; VOp, ventralis oralis posterior nucleus; nDRTT, non-decussating dentato-rubral-thalamic tract.

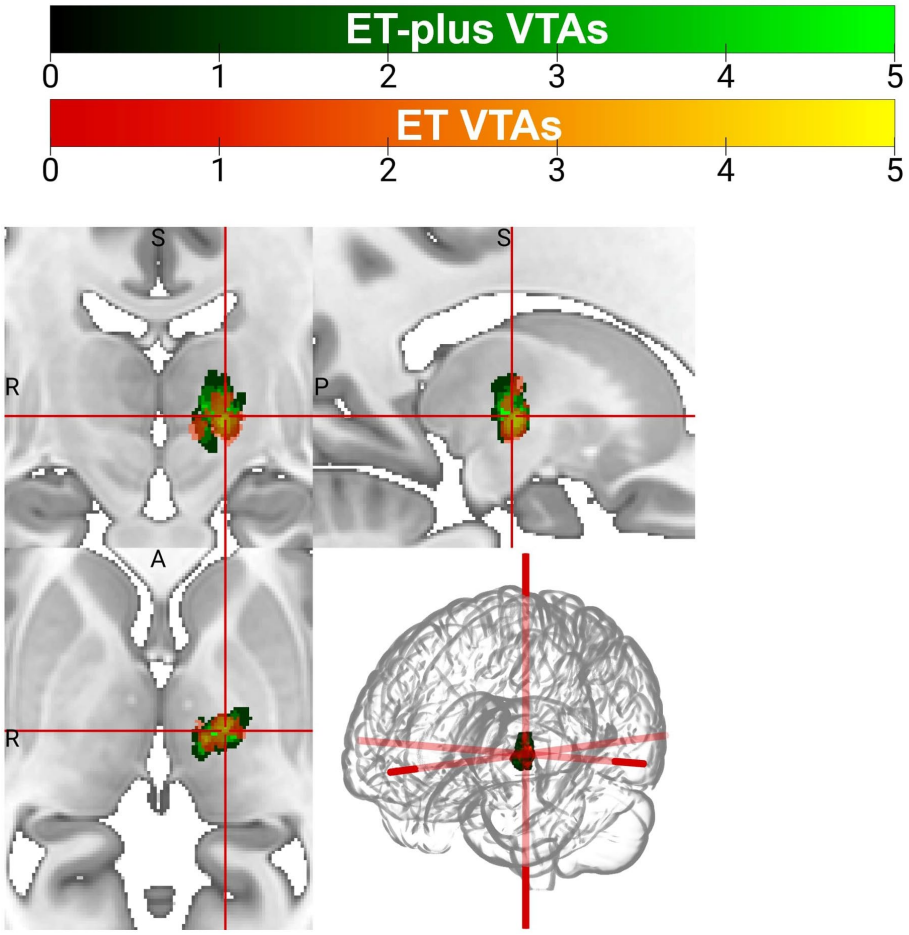

FIGURE 2
Volume of tissue activated (VTA) heatmap for patients with ET (orange) and ET-plus (green).

Dystonia was the more prevalent plus feature in the ET-plus subgroups. VTA analysis for ET-plus subgroups was carried out specifically for ET-plus with dystonia ($n = 20$) and ET-plus with ataxia ($n = 9$) (Figure 5). ET-plus with dystonia has a slightly more medial optimal VTA connectivity compared to ET-plus with ataxia.

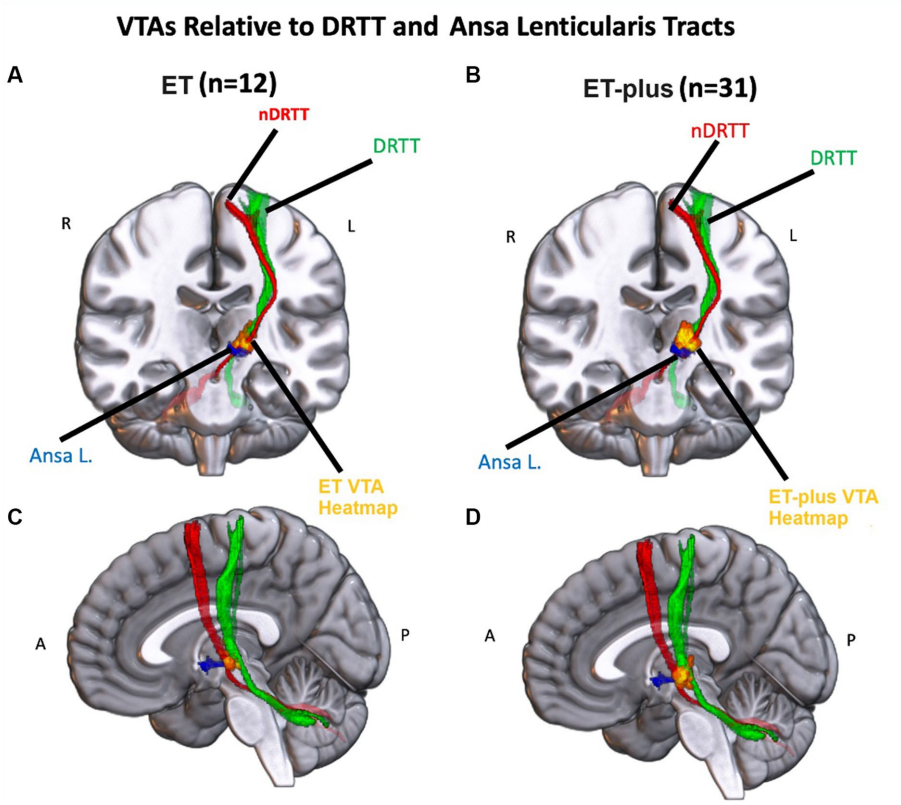

FIGURE 3
Left: Heatmap of the ET VTAs (red-yellow) relative to the nDRTT (red), the DRTT (green) and the Ansa Lenticularis (blue) in a coronal **(A)** and sagittal **(C)** view of an MNI-152 brain. Right: Heatmap of the ET+ VTAs (red-yellow) relative to the nDRTT (red), the DRTT (green) and the Ansa Lenticularis (blue) in a coronal **(B)** and sagittal **(D)** view of an MNI-152 brain.

Discussion

Our study aimed to delineate effective stimulation sites in ET and ET-plus patients, under the hypothesis that optimal VTA for each cohort would be distinctly different in the ventral thalamus, suggesting different underlying pathophysiologic mechanisms. This is the first study to further evaluate ET-plus subtypes, focusing on dystonia and ataxia as distinctly different from ET. Our cohort had more ET-plus patients compared to ET patients, with 87.5% of patients being re-classified to ET-plus, similar to recent literature reporting up to 50–83% of ET patients being reclassified to ET-plus (Prasad and Pal, 2019; Bellows and Jankovic, 2021). Our data found that VIM DBS is effective in both ET and ET-plus patients with comparable outcome, again in line with recent retrospective studies (Steffen et al., 2020; Gilmour et al., 2021). Clinically optimized VTAs were estimated to be within the same region of the ventral thalamus for ET and ET-plus patients in our data. While there were subtle differences in the ET and ET-plus COG analysis, where ET-plus COG was slightly more dorsal, presumably influenced by having more patients with dystonic features, we do not believe this result was clinically significant and should be interpreted with caution. Within ET-plus cohort, we further analyzed ET-plus with dystonia ($n = 20$), and ET-plus with ataxia ($n = 9$). ET-plus with dystonia subgroup has a more medially placed COG compared to that of ET-plus with ataxia, with unclear clinical significance. In addition, COG location relative to the DRTT showed that the VTAs for ET and ET-plus cohorts overlap significantly with this tract, which is likely the main contributor of tremor suppression as demonstrated in prior studies (Al-Fatly et al., 2019; Middlebrooks et al., 2021).

The new classification of ET-plus remains controversial as interpretations for neurologic soft signs can be subjective and the designation was not based on any neuroimaging, genetic or pathologic basis (Louis et al., 2020). A post-mortem study by Gionco et al. comparing ET and ET-plus patients did not demonstrate any pathologic differences (Gionco et al., 2021), further bringing into question whether ET and ET-plus are two distinct entities or a continuum of the same condition. Our study did not demonstrate a different optimal VTA site between ET and ET-plus, but our data further support a common tremor network between ET and ET-plus as demonstrated by Middlebrooks et al. (2021). A small matched retrospective study by Tsuboi et al. showed that dystonic tremor has an optimal connectivity between the VIM and VOp border (Tsuboi et al., 2021), related to stimulation of the pallidothalamic fibers. This finding may also explain how the VTA connectivity for ET-plus with dystonia was more medial in our subgroup analysis but there's insufficient evidence to suggest an alternative DBS target. While the 2018 consensus classification aimed to reduce heterogeneity in ET patients, ET is widely known for being a heterogeneous condition. In addition, it is increasingly

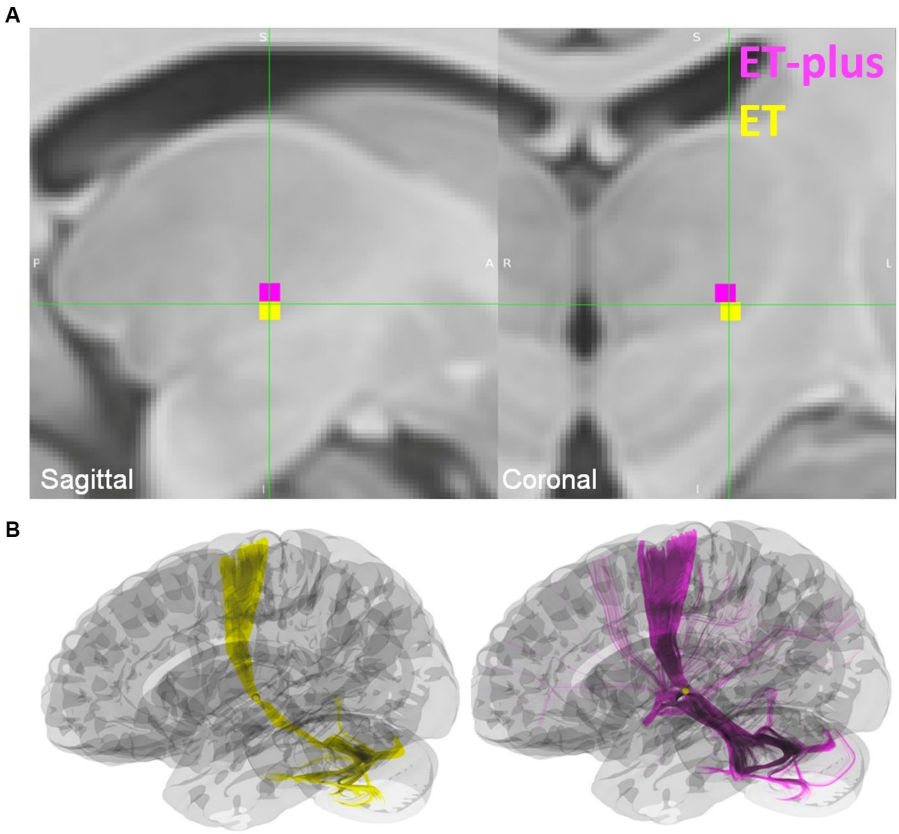

FIGURE 4
(A) Center of gravity (COG) analysis for ET shown in yellow, and ET-plus shown in magenta. **(B)** Location of the ET and ET-plus COG in relation to DRTT.

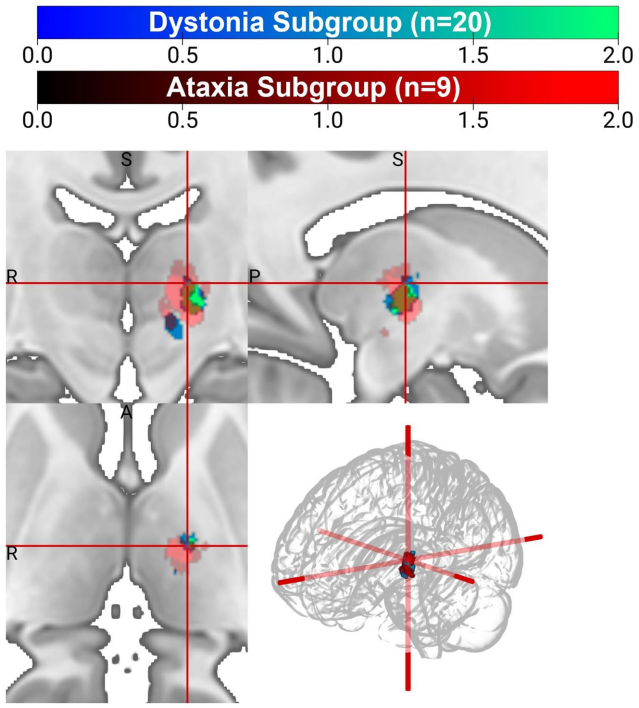

FIGURE 5
VTA heatmap for ET-plus dystonia (red) and ET-plus ataxia (blue-green).

apparent that ET is a dynamic syndrome and patients often evolve to have additional plus signs as their symptoms progress (Prasad and Pal, 2019; Louis et al., 2020; Bellows and Jankovic, 2021). A major limitation of the new consensus designation is the lack of objective measures for neurologic soft signs. Our study was also limited by having only one movement disorders specialist subjectively evaluate for video evidence of additional neurologic soft signs. It can be challenging to visually discern subtle posturing due to age-related or arthritic changes from dystonic posturing. A systematic review employed Bayesian analysis to estimate the probability of a patient having ET or ET-plus showed that having two or more soft signs makes an alternative diagnosis than ET more likely (Elble, 2022). The author also proposes additional diagnostic considerations to further distinguish ET from ET mimics such as utilizing electrophysiology to rule out enhanced physiologic tremor (EPT) or employing somatosensory temporal discrimination threshold to discern ET from dystonia (Elble, 2022). Future prospective studies with larger sample size, more stringent and objective assessments of different neurologic soft signs with correlating outcome measures (i.e., ET-plus with dystonia, ET-plus with ataxia, or ET-plus with cognitive impairment) may shed more light into differentiating ET-plus subtypes.

Due to the retrospective design, our data only captured specific connectivity snapshots, with a wide range of follow-up periods considering patients who were later enrolled into the study. It is difficult to confirm whether there were subtle changes in optimal

stimulation sites over time as patients' symptoms evolve. Similarly, changes within VTA overlaps due to habituation or disease progression were not well captured in this study. A prospective, longitudinal study with evaluations at regular intervals may help us better understand the difference between ET and ET-plus, and even bring more insights into ET disease progression. Our study has additional limitations: the sample size was drastically reduced due to loss of pre-operative videos, most subjects had bilateral VIM implants, which may affect optimal stimulation parameters to avoid stimulation-induced side effects, VTAs were recreated in MNI space and unable to account for subject's individual anatomic differences, there was no functional connectivity data available to corroborate for clinical tremor reduction, and this was not a blinded study.

Conclusion

VIM DBS therapy is efficacious in patients with ET and ET-plus. There were no significant differences in optimal stimulation site or VTA overlap with white matter fiber tracts between ET, ET-plus and ET-plus subgroups.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Health Sciences South Carolina (HSSC) electronic Institutional Review Board (eIRB number Pro00062817). Written informed consent for participation was not required for this study in accordance with the local legislation and institutional requirements.

Author contributions

CY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. DL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. CC: Data curation, Writing - review & editing. NR: Writing – review & editing, Resources. IT: Resources, Writing – review & editing. GR: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Unraveling the complexities of programming neural adaptive deep brain stimulation in Parkinson's disease

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Over the past three decades, deep brain stimulation (DBS) for Parkinson's disease (PD) has been applied in a continuous open loop fashion, unresponsive to changes in a given patient's state or symptoms over the course of a day. Advances in recent neurostimulator technology enable the possibility for closed loop adaptive DBS (aDBS) for PD as a treatment option in the near future in which stimulation adjusts in a demand-based manner. Although aDBS offers great clinical potential for treatment of motor symptoms, it also brings with it the need for better understanding how to implement it in order to maximize its benefits. In this perspective, we outline considerations for programing several key parameters for aDBS based on our experience across several aDBS-capable research neurostimulators. At its core, aDBS hinges on successful identification of relevant biomarkers that can be measured reliably in real-time working in cohesion with a control policy that governs stimulation adaption. However, auxiliary parameters such as the window in which stimulation is allowed to adapt, as well as the rate it changes, can be just as impactful on performance and vary depending on the control policy and patient. A standardize protocol for programming aDBS will be crucial to ensuring its effective application in clinical practice.

KEYWORDS

Parkinson's disease, deep brain stimulation, closed loop, adaptive, beta, subthalamic nucleus (STN), globus pallidus internus (GPi)

Introduction

Deep brain stimulation (DBS) currently offers effective treatment for motor symptoms in Parkinson's disease (PD). However, despite its success, it still suffers from several weaknesses. These include impairment of speech, only moderate effectiveness for freezing of gait, some residual fluctuation between on/off states, and loss of efficacy over time for axial symptoms and to a lesser extent bradykinesia (Zibetti et al., 2011; Rizzone et al., 2014). Advancements in current steering, stimulation patterns, and other aspects of DBS offer the potential to improve its effectiveness for PD and other indications. One of the most promising advancements is the implementation of closed loop or adaptive DBS (aDBS) in which stimulation parameters, typically amplitude, modulate in response to a relevant biomarker

(Neumann et al., 2023). The hope of such a "smart" DBS approach is to improve symptom control, lessen side effects, and potentially lessen long-term habituation.

The first aDBS work in PD in 2013 used patients with externalized leads between the first and second stage of their DBS procedure (Little et al., 2013). This work showed the initial feasibility and efficacy of an aDBS approach for PD motor symptoms. aDBS using patients with externalized leads was expanded to longer duration sessions and freely moving humans (Rosa et al., 2015; Arlotti et al., 2018), and a patient with chronic DBS (Piña-Fuentes et al., 2017). The advent of the first-generation sensing neurostimulator, Activa™ PC+S, allowed for the advancement from externalized lead patients to aDBS in chronically implanted individuals using a computer-in-the-loop system. With this device, we demonstrated safety, tolerability and efficacy of aDBS (Velisar et al., 2019), and, subsequently, demonstrated the feasibility of aDBS for freezing of gait (Petrucci et al., 2020b). The availability of the Summit® RC+S for research expanded the opportunity for aDBS by both increasing its technological capabilities (e.g., biomarker selection, parameter adjustment, sampling frequency, etc.) as well as allowing implementation outside the clinic, thus allowing for aDBS at-home for the first time (O'Day et al., 2020a; Petrucci et al., 2020a; Gilron et al., 2021a; Oehrn et al., 2023). The combination of the research with Activa™ PC+S and Summit® RC+S led to the Percept™ PC, which became the first commercially available DBS neurostimulator for PD to offer neural sensing capabilities (Jimenez-Shahed, 2021). The Percept™ PC also offers the capability to perform chronic aDBS in research environments. These capabilities are being tested in a pivotal international multi-site trial, which, if successful, would allow for aDBS to become a clinical option for treatment.[1]

The rapidly approaching future in which aDBS is a viable clinical option brings with it the need to better understand how it should be implemented to maximize its benefits. Just as current DBS programming has evolved to a standardized protocol, a standardization for parameter selection and evaluation for aDBS will allow the optimization of therapy. The goal of this perspective article is to offer a guide for the considerations of aDBS calibration based on our research experience across the Activa™ PC+S, Summit® RC+S, and Percept™ PC (Medtronic PLC).

Sense-friendly configuration and restrictions

Older DBS leads had 4 cylindrical electrode contacts whereas current leads have 8 electrode contacts, 6 of which are segmented over 2 levels to allow for directional stimulation fields. One of the critical requirements for aDBS for most devices is a sense-friendly configuration that allows for recording of artifact-free local field potentials (LFPs) from the site of stimulation as a signal for aDBS. One of the main techniques for removing the stimulation artifact is through common mode rejection in which a "sandwich" is used by recording from the contacts surrounding the active stimulation contact(s) (Stanslaski et al., 2012, 2018). By taking the difference between the two recording contacts surrounding the active stimulation contact, the stimulation artifact is significantly attenuated, assuming similar impedances (**Figures 1A, B**). This configuration is possible if either a single contact at the second or third levels is active (single monopolar configuration) or if two contacts at the second and third levels are active (double monopolar configuration). However, this excludes certain configurations from being used for aDBS, such as those requiring the most dorsal or ventral contact. This limitation has been addressed by the AlphaDBS® system which allows for asymmetrical sensing configurations (Arlotti et al., 2021).

Typically, most targeting approaches for the subthalamic nucleus (STN) or globus pallidus internus (GPi) seek to have the electrodes at the second and/or third levels placed within the target of interest, and therefore, not surprisingly, these contacts are the ones most often used as active contacts (Hamel, 2003). However, a variety of circumstances may require the use of the most dorsal or ventral contacts. Ventral contacts may be used to treat gait impairment, and dorsal contacts may be used to treat dyskinesias (Alterman et al., 2004; Herzog et al., 2007; Chastan et al., 2008; Weiss et al., 2013; Ramdhani et al., 2015). Additionally, activation of the most dorsal or ventral electrode may be required in cases of suboptimal targeting.

Adaptive deep brain stimulation (aDBS) does not necessitate that both sides have sense-friendly configurations, as aDBS can be set up in one hemisphere, while maintaining the other side on open loop DBS, or signal from one hemisphere can be used to drive aDBS in both hemispheres.

Even sense-friendly configurations can still be vulnerable to various sources of artifact that render the LFP unusable (Thenaisie et al., 2021; Hammer et al., 2022). Artifact can still be seen if there is significant mismatch in impedances between the two recording contacts surrounding the active electrode (Stanslaski et al., 2012), or if there is a mechanical issue along the extension or lead (e.g., a break, fluid intrusion, etc.). Additionally, electrocardiogram (ECG) artifact can be a source of noise, especially in lower frequencies and if the implantable pulse generator (IPG) is implanted in the left chest (Neumann et al., 2021; Thenaisie et al., 2021). LFPs are especially vulnerable to ECG artifacts during passive recharge due to an increased duration of time after each stimulation pulse in which ECG or other sources of noise can leak into the signal (Stanslaski et al., 2018). Movement, especially turning of the head or standing up, can, in some instances, elicit transient artifacts (Thenaisie et al., 2021; van Rheede et al., 2022). Lastly, ramping of stimulation is known to cause transient artifacts (Ansó et al., 2022; Hammer et al., 2022). Separating the recording and stimulation site, such as the use of cortical electrocorticography (ECoG), offers an alternative to minimize the impact of DBS-related artifacts on the signal of interest, but is not standard of care (Swann et al., 2018; Gilron et al., 2021a; Oehrn et al., 2023).

One potential future approach to avoid potential artifacts in the neural data and sensing configuration restrictions is to instead adapt stimulation based on measurements of the symptoms directly from peripheral sensors. Inertial measurement units (IMUs) with gyroscopes and accelerometers have successfully been used to detect and measure tremor, freezing of gait, bradykinesia, and dyskinesias (Griffiths et al., 2012; Braybrook et al., 2016; O'Day et al., 2020b; Powers et al., 2021). A system that enables Bluetooth

1 https://clinicaltrials.gov/ct2/show/NCT04547712

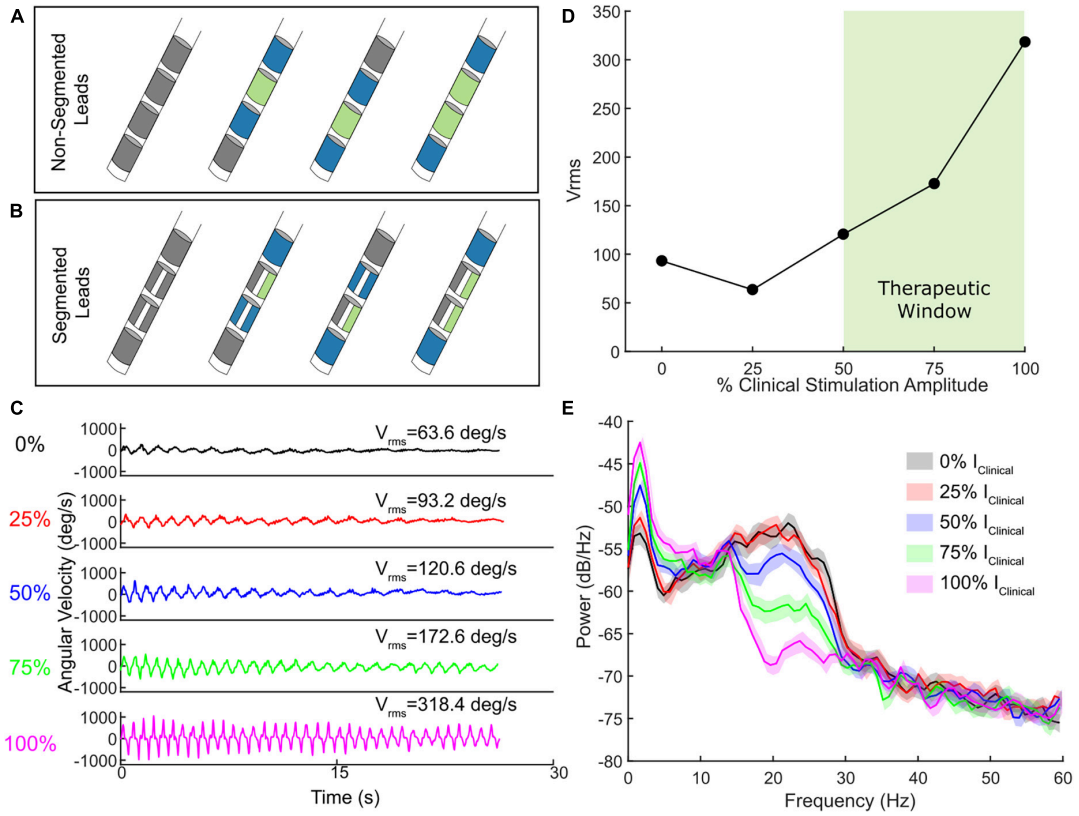

FIGURE 1
(A) Schematic of four contact lead sense-friendly configurations. Blue contacts represent potential recording pairs and green contacts represent stimulating contacts. **(B)** Schematic of eight contact directional lead sense-friendly configuration. Directional leads allow the ability to stimulation with one, two, or all three segments in a given row. Only one example of an active segmented contact is shown. **(C)** Example of a wrist flexion-extension task which quantitatively measures bradykinesia at different levels of stimulation intensity relevant to clinical stimulation. **(D)** The observed Vrms across the different stimulation levels, with the therapeutic window highlighted in light green. **(E)** The accompanying power spectral density plots for one STN for the wrist flexion-extension task shown in **(C)** at the different levels of stimulation intensity.

communication between an external sensor and the IPG could therefore allow the ability to adapt stimulation in response to the presence or severity of various symptoms rather than relying on, or in addition to, a neural biomarker. Alternatively, sensors could be directly integrated into the IPG itself for a fully embedded system. Pilot studies have demonstrated the feasibility of this approach (Malekmohammadi et al., 2016; O'Day et al., 2020a; Cernera et al., 2021; Melbourne et al., 2023) but this capability is currently limited to research devices.

Identifying the neural input for aDBS

There have been several approaches to selecting which signal to use as input for aDBS in PD. A relevant neural input for aDBS should ideally meet 2 specific criteria: 1, it should relate to the behavioral impairment and 2, it should be modulated by DBS in an expected and consistent manner. These two criteria ensure that the neural input is both a good biomarker of the underlying pathophysiology of the disease, and an appropriate feedback signal, so that when stimulation amplitude adjusts, it leads to corresponding changes in the biomarker.

The most commonly used neural signal for aDBS is LFP beta band (13–30 Hz) power recorded from the DBS lead, since the greater the attenuation of beta power or reduction in beta burst duration from DBS, the greater the improvement in bradykinesia, rigidity, gait impairment, and freezing of gait (FOG) (Kuhn et al., 2008; Neumann et al., 2016; Anidi et al., 2018; Kehnemouyi et al., 2021). Beta burst durations and gamma power have also been used as relevant and efficacious neural inputs, and newer methods have leaned on machine learning approaches to determine the biomarker of interest rather than *a priori* designations (Swann et al., 2018; Petrucci et al., 2020a; Gilron et al., 2021a; Merk et al., 2022; Gao et al., 2023; Oehrn et al., 2023).

Regardless of choice of biomarker, it is critical that there is sufficient signal to rely on it for aDBS. Large datasets from OR and postoperative recordings indicate the presence of beta power within the STN in a significant percentage of individuals with PD (Shreve et al., 2017; Darcy et al., 2022). The BrainSense capabilities of the Percept^{TM} PC device allow evaluation of beta power across all contact pairs OFF DBS in chronically implanted patients to determine whether enough signal is present to use for aDBS. The choice of stimulation contact can then be chosen based on the highest observed beta power. The Percept^{TM} PC device offers the ability to use a 5 Hz band around the frequency of maximum observed beta power (or frequency band of interest) as the input for aDBS.

Once the biomarker of interest has been established for a given patient, there are multiple approaches for the control policy. The two most common policies are a single-threshold and dual-threshold approaches (**Supplementary Figure 1**). In the single-threshold approach, stimulation will increase when the biomarker is above threshold, and decrease when the biomarker is below threshold (Little et al., 2013, 2016; Piña-Fuentes et al., 2020). This response to threshold can also be inverted in the case of gamma power. Whereas increased beta is often associated with greater PD impairment, increases in gamma power in the motor cortex and STN have been linked to the presence of dyskinesias and a hyperkinetic state (Swann et al., 2016; Oehrn et al., 2023), which is a sign of excessive combined therapy between DBS and medication. Therefore, stimulation decreases in response to gamma power going above threshold (Oehrn et al., 2023). Meanwhile, in a dual-threshold approach, there are two thresholds, which creates a 3rd "hold" state. In this policy, when the biomarker (e.g., beta power) is above the upper threshold stimulation increases, whereas if it is below the lower threshold, stimulation decreases, but if it is between thresholds, stimulation holds (Velisar et al., 2019).

Determining safe and efficacious aDBS amplitude limits

Standard DBS requires determining the amplitude at which stimulation remains constant, whereas aDBS requires setting safe and efficacious minimum and maximum amplitude limits, between which aDBS varies. Most early aDBS research allowed the minimum amplitude to be at zero (Little et al., 2013, 2016; Velisar et al., 2019; Piña-Fuentes et al., 2020; He et al., 2023). However, as the research into the efficacy of aDBS has evolved, it is now evident that setting a non-zero, therapeutically acceptable, minimum limit for aDBS amplitude can protect against lowering aDBS amplitude to sub-therapeutic levels, which may result PD symptom return, especially tremor (Velisar et al., 2019; He et al., 2023). The upper stimulation amplitude is that above which there may be side effects due to over stimulation such as dyskinesias, face pulling, speech intelligibility, or paresthesias. Accurate determination of these limits is crucial for ensuring therapeutic level of stimulation during aDBS.

The growing accessibility of wearables (e.g., IMUs) and measurement devices offers the opportunity to determine safe and efficacious lower and upper limits of stimulation. For instance, angular velocity, accelerometry, and other forms of behavioral data can be used to provide high-resolution quantitative metrics of behaviors and symptoms to aid clinicians evaluating the therapeutic range of DBS in a patient. Amplitude titrations where behavior is assessed at randomized presentations of various intensities can provide a clear picture for patient-specific lower and upper limits for aDBS with a therapeutic response (i.e., therapeutic window). For instance, an instrumented assessment of bradykinesia with DBS titrations can allow for the identification of the minimum level of stimulation that provides therapeutic benefit (**Figures 1C, D**). These titrations can also be used for assessment of other symptoms such as tremor or gait impairment (**Supplementary Figure 2**). Combining DBS titrations with high-resolution wearables and/or measurement devices that provide digestible reports of behavior in near real time can both automate and reduce the time needed for determining stimulation limits for aDBS.

Deep brain stimulation (DBS) titrations offer the additional benefit of evaluating how the neural biomarker of interest responds to DBS within the aDBS amplitude limits (**Figure 1E**). Although it is important to identify the presence of a biomarker (e.g., beta power) OFF DBS, it is important to confirm that it also modulates with incremental adjustments of DBS. Both single and dual threshold control policies hinge on the assumption that beta (or the frequency band power of interest) modulates in an expected manner. Therefore, one must ensure both that the band chosen is not inert and that there is sufficient modulation specifically within the aDBS limits (i.e., I_{min} to I_{max}) as that is where stimulation will be during aDBS. If not, then aDBS will simply be adapting primarily on noise, rather than the pathophysiological marker. This modulation should be relatively continuous in fashion if stimulation amplitude is adapted in a graded manner. An alternative viable approach is if the biomarker modulates in a binary fashion (e.g., present of absent) when combined with adapting between two stimulation states (e.g., lower level and higher level of stimulation amplitude).

The inverse relationship between beta power and DBS amplitude enables the choice of beta power thresholds directly from the choice of I_{min} and I_{max}. For the dual threshold algorithm, the upper beta threshold is set at the beta power that is measured during DBS at I_{min}; the lower beta threshold is either that measured during DBS at I_{max} or a value midway between beta power at I_{min} and that at I_{max} (Velisar et al., 2019). The beta threshold for single threshold aDBS has been traditionally chosen as 75% of beta power OFF DBS. Arbitrarily deciding these thresholds independent of how the neural biomarker responds to DBS amplitude may lead to suboptimal adaptation. Medication further complicates the decision of thresholds since medication also attenuates beta. Typically, thresholds are identified first off medication, and then altered, if necessary, when tested on medication. This may involve lowering the beta threshold due to medication-induced reductions in overall beta power. Typically streaming the data during aDBS setup allows confirmation of whether there is sufficient modulation with aDBS or if lowering of the beta threshold is required, as would be the case if stimulation amplitude plummeted to I_{min} in the presence of medication.

Although these biomarkers are typically evaluated in clinic, many of these signals vary with activity and over the course of the day and night (Fleming et al., 2022; van Rheede et al., 2022; Feldmann et al., 2023). Therefore, future work may establish the validity of combining these in-clinic recordings with extended at-home recordings to find the biomarker of interest, and understand its relation to, activity, sleep and circadian rhythms (Toth et al., 2020; Gilron et al., 2021b; Smyth et al., 2023).

Ramp rate evaluation

After establishing the biomarker, control policy and thresholds for aDBS, and window to allow stimulation to adjust within, the last critical decision is how fast or slow to allow stimulation to change (i.e., ramp rate). Determining the ramp rate is both goal- and patient-specific. The ramp rate and control policy used go

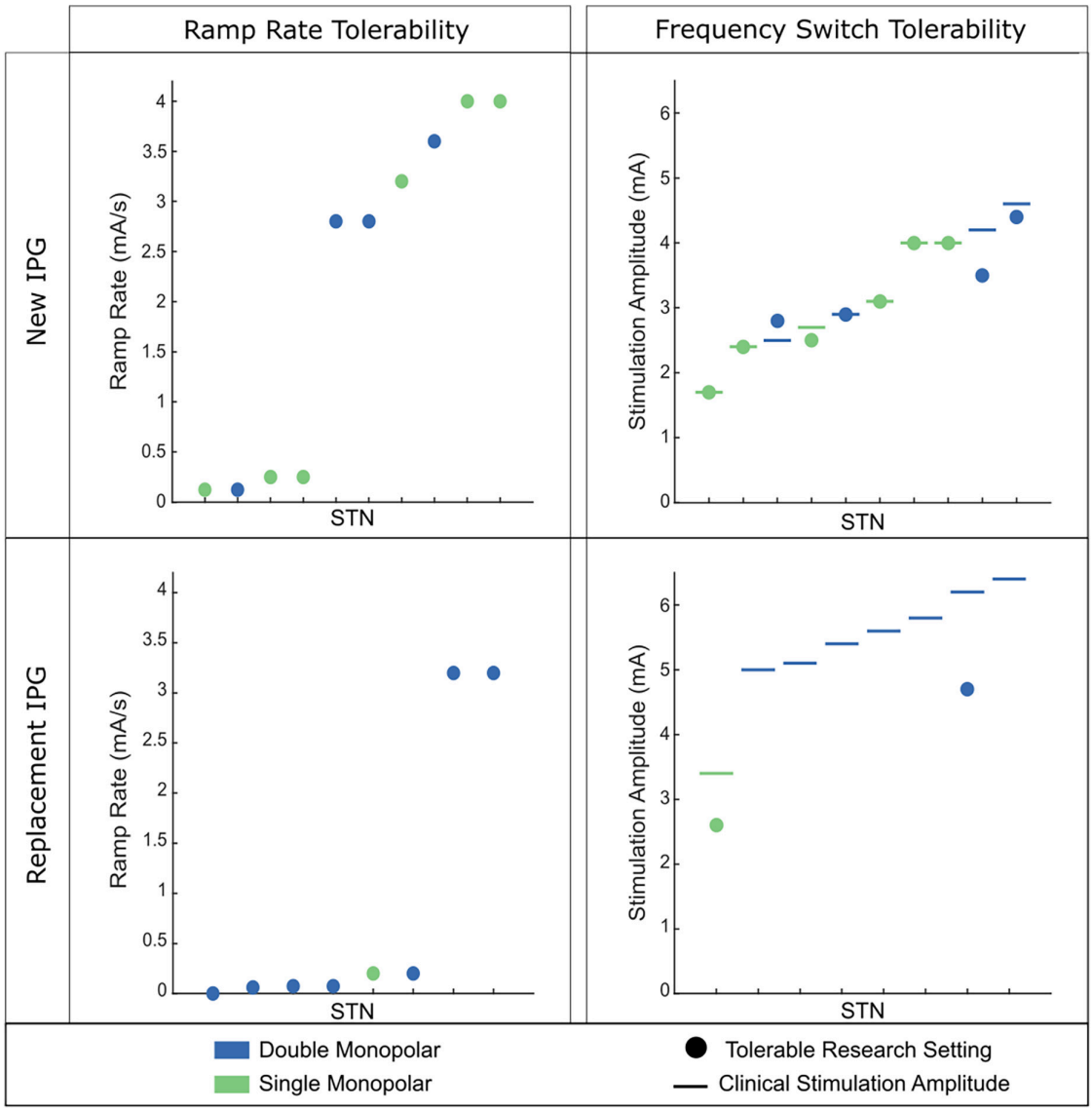

FIGURE 2
Tolerability of ramp rate across 18 STNs (9 individuals). **(Left)** Observed tolerability for ramp rate of stimulation intensity. **(Right)** Observed tolerability of instantaneous frequency switching between 140 and 60 Hz. The participant's clinical stimulation is represented by the horizontal line. The circle depicts the tolerable amplitude found for frequency switching. If no circle is present, no tolerable therapeutic amplitude was found for frequency switching. **(Top)** Patient cohort who are on their first IPG. **(Bottom)** Patient cohort who have had at least one IPG replacement. Green dots indicate the patient had a single monopolar stimulation configuration and blue dots indicate a double monopolar stimulation configuration. Patients on their first IPG showed better tolerability of faster ramp rates of intensity and higher amplitudes for frequency switching. Patients on replacement IPGs rarely tolerated fast ramp rates of intensity or instantaneous frequency switching.

hand-in-hand. For instance, single-threshold control policies are often combined with rapid ramp rates to quickly provide maximum amount of stimulation to respond to the biomarker. Typically, these rapid rates attempt to traverse from I_{min} to I_{max} in roughly 250 ms (e.g., 8 mA/s if traversing a 2 mA range) (Little et al., 2013). When using this rapid ramp rate, initial single-threshold policies typically fluctuated between 0 mA and I_{max} with a goal of stimulation being active roughly 50% of the time. However, it may be beneficial to use an I_{min} rather than dropping stimulation all the way to 0, as discussed earlier. Dual-threshold control policies are often used for slow time courses, such as adjusting stimulation based on medication-induced fluctuations which occur on the order of minutes to tens of minutes) or intermediate time courses on the order of seconds (0.1–0.25 mA/s) (Velisar et al., 2019). Sometimes faster ramp ups in comparison to ramp down (e.g., 2× faster) are implemented to bias toward higher therapy and protect against stimulation dropping too fast.

Although one may have a target ramp rate to use based on the specific goal of aDBS, the ramp rate used is patient-specific as there is large variability among what is tolerated. Ramping too fast can elicit symptoms such as paresthesia or nausea that may make aDBS intolerable. These symptoms tend to be most prevalent when stimulation is increasing and at the top of the stimulation range (Petrucci et al., 2021). The observed variability in patient-tolerability may be due to a host of factors, including max amplitude of stimulation, size of the range that stimulation

is traversing, number of contacts active (e.g., single vs. double monopolar), electrode location within the target, impairment level and disease severity, and how long a patient has been on DBS (Koeglsperger et al., 2019). In our experience, less impaired patients on their first DBS IPG tend to be much more tolerable to rapid ramp rates (**Figure 2**). Meanwhile, more impaired patients who have been on DBS much longer (e.g., have had one or multiple IPG replacements), require higher amplitudes, and often double monopolar configurations tend to not be able to tolerate fast ramp rates or, in some instances, any ramping at all. Similar variability was observed when altering different stimulation parameters, such as instantaneous frequency switching between 140 and 60 Hz (**Figure 2**).

Despite the variability in ramp rate tolerability among patients, there are several approaches that can be used to try and achieve tolerability. These include lowering I_{max} and/or slowing down the rate. The decision of which of these two approaches to take will depend on the goal of the aDBS and the patient. For more impaired individuals, lowering I_{max} may not be a viable option as the patient needs more stimulation for therapeutic benefit. Therefore, the main option would be to simply slow down the ramp rate until achieving tolerability (and perhaps only adapt one side if it is found that only one side is contributing to the side effects). Meanwhile, in a less impaired patient lowering I_{max} may prove more beneficial if it means a more rapid ramp rate can be implemented that can get the person on high levels of stimulation quicker.

Potential shortcomings, solutions, and alternative approaches

The growing availability of aDBS offers exciting promise for the therapeutic potential of DBS, but there are several potential shortcomings. Although beta power has been identified as a potential useful biomarker for aDBS due to its relation to bradykinesia and rigidity alongside its responsiveness to DBS and medication, it may not be a suitable for everyone. Tremor and voluntary movement have both been shown to attenuate beta, which may lead to unwanted decreases in stimulation amplitude (Quinn et al., 2015; Shreve et al., 2017; Velisar et al., 2019; Eisinger et al., 2020). However, there are potential workarounds to combat this. For instance, ensuring that the lower stimulation limit (i.e., I_{min}) is set at a high enough stimulation amplitude where tremor is sufficiently controlled can ensure that stimulation will maintain therapeutic efficacy for tremor even with drops in beta power. Similarly, one can protect against voluntary movement-related attenuation in beta by requiring a sufficient onset duration (i.e., the amount of time required for the biomarker to be above or below threshold before making a stimulation decision). Reduction in beta power is most strongly association with the initiation of movement, so onset durations $>$ 1 s can ensure transient movement-related reductions in beta do not lead to inadvertent decreases in stimulation. A potential long-term solution to both problems is the identification of alternative biomarkers, but this may be challenging with the current hardware limitations.

It is important to recognize that aDBS is just one of several possible approaches to deal with some of the limitations of current DBS. Side effects from DBS may also be avoided with directional current steering, which allows more efficient targeting of the region of interest without spillover to neighboring regions that elicit common side effects such as dysarthria (Timmermann et al., 2015; Dembek et al., 2017; Umemura et al., 2023). Similarly, more precise understanding of the anatomy through high-resolution imaging can enable identification of sweet spots for different symptoms within the STN or GPi (Hilliard et al., 2011; Dembek et al., 2019; Horn, 2019). Coupling this anatomy with directional steering may allow for better treatment for refractory symptoms such as freezing of gait. Alternative stimulation approaches, such as coordinated reset or theta burst stimulation (Wang et al., 2016; Horn et al., 2020), may also provide a different approach for treatment refractory symptoms. These approaches can be implemented independently or combined with aDBS. For instance, current directional leads offer the potential to combine current steering with aDBS, but it is still too early to know how feasible this approach may be.

Conclusion

aDBS offers an exciting advancement for current DBS technologies. Although, it will require tuning more parameters than traditional continuous open loop DBS, a standard and logical protocol makes aDBS set up straightforward. The initial choice of the active electrodes is made simpler than the previous method of monopolar review by the capability to sense beta power from all the available electrodes: substantial evidence has shown that the active electrode that is closest to the site of maximum beta power has the best therapeutic outcome. In this Perspective we have outlined several of the key considerations for implementing aDBS based on our research and clinical experience with the Activa™ PC+S, Summit® RC+S, and Percept™ PC.

Implementing aDBS first requires a sense-friendly stimulation configuration and the presence of a viable biomarker to serve as the neural input for aDBS. A relevant neural input should both relate the behavioral impairment and modulate with DBS amplitude in an expected and consistent manner. The most popular neural input to date for PD is beta power due to its presence in PD, relation to impairment levels, and modulation by DBS intensity. In addition to the neural input, accurate determination of the window in which stimulation will adjust within is crucial for maintaining acceptable therapeutic efficacy with aDBS. Ideally this window should be determined quantitatively with either wearable sensors or measurement devices that can accurately show the lower and upper limits of stimulation that provide therapeutic benefit without adverse side effects but this can also be done using clinical assessment. The establishment of the lower and upper limits should go hand in hand with the thresholds that are used for the neural control policy, as aDBS will be modulating within the defined amplitude window based on the observed biomarker.

The goal of aDBS will impact both the control policy choice (e.g., single- or dual-threshold) as well as the rate as which stimulation amplitude should adjust. It is worth noting that the field is still in the early stages of understanding how tuning of these various parameters impacts overall performance. The development of optimization strategies for simplifying these decisions and

understanding which parameters most impact overall performance will be critical for wide-level successful adoption. Additionally, future devices may expand this space even further as aDBS increases in sophistication, such as developing to adapt other stimulation parameters besides amplitude (e.g., frequency, pulse width, active contact, etc.), respond to more sophisticated neural biomarkers besides just power in a frequency band as well as access to higher frequencies, and ability to run aDBS based on other non-neural signals such as those from peripheral sensors or embedded sensors in the IPG itself.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Stanford Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KW: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. JM: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. PA: Conceptualization, Data curation, Formal analysis, Writing – review & editing. HB-S: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1310393/full#supplementary-material

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Improving naturalistic neuroscience with patient engagement strategies

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Introduction: The clinical implementation of chronic electrophysiology-driven adaptive deep brain stimulation (DBS) algorithms in movement disorders requires reliable representation of motor and non-motor symptoms in electrophysiological biomarkers, throughout normal life (naturalistic). To achieve this, there is the need for high-resolution and -quality chronic objective and subjective symptom monitoring in parallel to biomarker recordings. To realize these recordings, an active participation and engagement of the investigated patients is necessary. To date, there has been little research into patient engagement strategies for DBS patients or chronic electrophysiological recordings.

Concepts and results: We here present our concept and the first results of a patient engagement strategy for a chronic DBS study. After discussing the current state of literature, we present objectives, methodology and consequences of the patient engagement regarding study design, data acquisition, and study infrastructure. Nine patients with Parkinson's disease and their caregivers participated in the meeting, and their input led to changes to our study design. Especially, the patient input helped us designing study-set-up meetings and support structures.

Conclusion: We believe that patient engagement increases compliance and study motivation through scientific empowerment of patients. While considering patient opinion on sensors or questionnaire questions may lead to more precise and reliable data acquisition, there was also a high demand for study support and engagement structures. Hence, we recommend the implementation of patient engagement in planning of chronic studies with complex designs, long recording durations or high demand for individual active study participation.

KEYWORDS

deep brain stimulation, patient engagement, Parkinson's disease, neurophysiology, home monitoring, naturalistic monitoring

Introduction

Deep brain stimulation (DBS) is an effective therapy for movement disorders. Besides its clinical relevance for symptom alleviation, DBS enables electrophysiological recordings from pathophysiologically relevant deep brain structures. Especially for Parkinson's disease (PD), DBS led to knowledge about symptom-specific electrophysiological signatures (Brown and Thompson, 2001; Kühn et al., 2006; Tinkhauser et al., 2017; Feldmann et al., 2022) applied as a feedback signal for personalized adaptive stimulation (aDBS) (Little et al., 2013; Arlotti et al., 2018; Velisar et al., 2019). First studies with clinical application of aDBS are under way (Caffi et al., 2023; Herrington et al., 2023). However, most physiomarker research to date has a limited ecological validity due to its highly controlled lab conditions and short recording durations. For ecologically valid, real-life (naturalistic) physiomarker data, additional data on patient wellbeing and symptom severity is necessary for data interpretation. For successful data collection, we implemented patient engagement in our study design. Here, we describe our perspective and experiences.

Parkinson's disease (PD) is a systemic disease characterized by heterogeneous motor and non-motor symptomatology that may require diverse aDBS-physiomarkers. Various factors besides solely symptom fluctuation will modulate these symptom-specific physiomarkers during normal life. Reliable symptomatic and electrophysiological monitoring for PD and DBS may not only answer urgent scientific questions, but also increase the accessibility of the emerging global PD patient care (Bloem et al., 2021), especially in medically underserved areas, e.g., by online therapy optimization in remote areas (Klucken et al., 2018; Bloem et al., 2020; Virmani et al., 2022). Therefore, a thorough understanding of the naturalistic variability of PD symptoms and its physiomarkers on an intra-day and inter-day level is important to establish aDBS paradigms. In our first experiences with naturalistic chronic subthalamic recordings, we demonstrated how factors like circadian periodicity and movement modulate the currently proposed PD-physiomarker (**Figure 1A**, top) (van Rheede et al., 2022). However, higher resolution analyses focusing on i.e., single medication-intake moments appeared to be less conclusive and would likely benefit from additional detailed symptomatic and contextual information (**Figure 1A**, bottom).

To elucidate this, we can collect symptomatic data in parallel to the chronic neural recordings in an active or passive manner. Active data requires an active patient involvement, such as completing a patient reported outcome (PRO) (Habets et al., 2020; Weizenbaum et al., 2022) or participating in a motor task, i.e., tapping task, (Zhan et al., 2018; Lipsmeier et al., 2022). Passive data collection is done unobtrusively via i.e., inertial measurement units (IMUs) containing kinematic sensors i.e., heart rate, or geolocation (Cornet and Holden, 2018; De Calheiros Velozo et al., 2022). For valid and meaningful data analysis, it is of key importance that the parallel data captures the relevant symptomatology reliably, contains essential contextual information on e.g., medication intakes, and above all, performs data acquisition as continuously as possible. For this, the primary necessity is study participant compliance. Hence, we believe we can only achieve high quality, active patient participation by involving those people during the study planning that are at the center of our research: the patients themselves.

Current literature

The inclusion of patients in the definition of research-agendas and study designs can improve studies' feasibility, cost-effectiveness, and validity (Schipper et al., 2014; Roudini et al., 2023). Sporadically, investigators pioneered patient engagement in PD studies and reported about this endeavor (Meinders et al., 2022; Evers et al., 2023). Meinders and colleagues recently published general advice and experiences with patient engagement in PD studies, but specific reports on patient engagement for naturalistic monitoring studies with DBS patients lack, to our best knowledge.

So far, only a few studies reported the implementation of patient engagement methods to improve home monitoring studies with PD patients. An international, multi-center study included PD patients and healthcare professionals to define the most important symptoms and concepts of activities of daily life (ADL) to monitor during daily life (Ferreira et al., 2015; Serrano et al., 2015). Based on 200 answered questionnaires and several Delphi rounds, the investigators concluded bradykinesia/hypokinesia, tremor, sway, gait, sleep, and cognition to be the most important symptoms to assess continuously. Recently another study reported on a detailed patient engagement exercise to develop a set of PRO-items, for both motor and cognitive domains, specifically tailored for early-disease-stage PD patients (Morel et al., 2023). The validation of these items is currently under investigation in follow-up research. The findings of these two studies using patient engagement did not majorly differ, which underlines the generalization of their results (Ferreira et al., 2015; Morel et al., 2023). This, however, does not mean that smaller patient engagement methods are not necessary anymore for specific PD populations. In general, investigators should repeat and check generalized assumptions around data-driven monitoring or prediction models when applying it on new (sub) populations (Kelly et al., 2019), as we will highlight later in this literature overview.

We will provide a brief overview of the current advances to monitor these symptoms both subjectively and objectively. We limit ourselves to methods that are specifically designed, or proven to be feasible, for naturalistic monitoring with a high temporal resolution.

Subjective assessments typically consist of PROs and patients should complete them on various temporal intervals, depending on the applied methodology. The best-known diary method is probably the Hauser diary, that differentiates between off- and on-dopaminergic states, with and without (burdensome) dyskinesia (Hauser et al., 2006). Although this method is successfully implemented for repetitive motor symptom assessment throughout a day (Rodriguez-Molinero et al., 2018), it does not provide specific information about all symptomatic items. To collect several specific symptom and functionality domains multiple times daily, ecological momentary assessments (EMA) are introduced and proven to be feasible

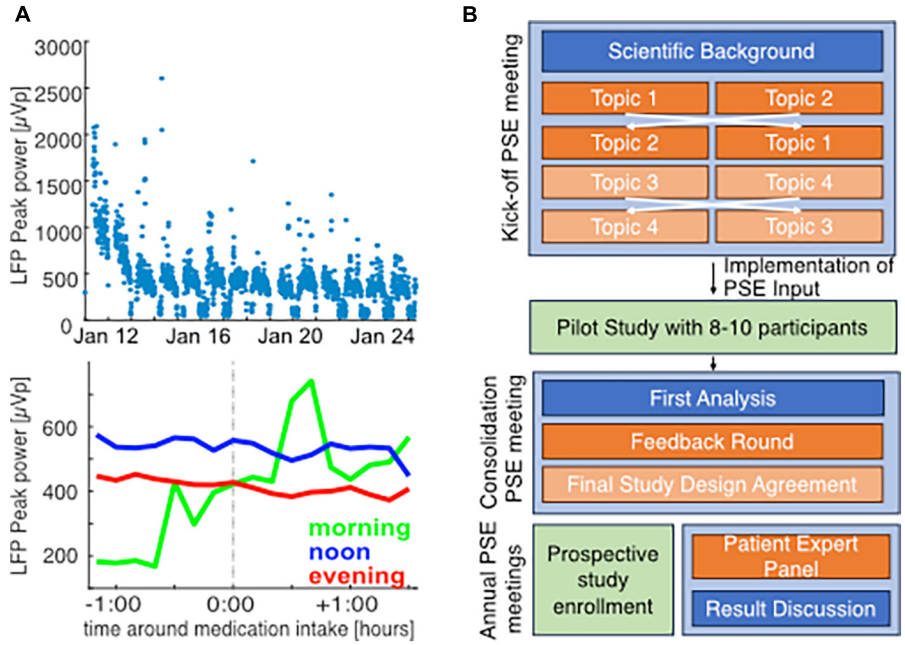

FIGURE 1
Challenges of chronic monitoring and concept for patient engagement in studies on naturalistic neuroscience in PD patients: single example for illustration of challenges in chronic biomarker acquisition in a 56-year old male PD patient with subthalamic DBS and peak biomarker recording at 22 Hz (right hemisphere). Data acquisition and analysis was performed as previously described [van Rheede et al., 2022; Feldmann et al., 2023, approved by the local ethics committee (EA2/256/60)] in parallel with clinical records at a post-operative rehabilitation. At a low-resolution of 3-days means, beta band suppression from the beginning toward the end of the stay reveals that clinical improvement through therapy optimization is also reflected in biomarker levels (start of rehab: 758.9 ± 400.7, end of rehab 273.96 ± 160.3, mean ± standard deviation), (**A**, top). However, higher resolution analysis of 10 min-mean beta band activity around medication intake based on clinical notes (mean for morning: 9, noon: 32, evening: 21 time points) does not lead to conclusive results and may be influenced by circadian rhythms (**A**, bottom). This demands better quality symptomatic documentation, that requires a high level of patient commitment. Therefore, we developed a patient engagement strategy **(B)**. Orange panels indicate active patient involvement throughout the study, blue panels indicate the scientific information discussed with patients, and green panels indicate the data acquisition phases.

for Parkinson monitoring (Heijmans et al., 2019; Habets et al., 2020). A second, independent group recently reproduced the feasibility of EMA for PD patients (Weizenbaum et al., 2022). Recent studies including patient experts revisited PRO-items resulting in general advises and two updated PRO instruments (Morel et al., 2023). Since these repetitive PRO methods have different sampling frequencies than the gold standard assessments, naturalistic validation is challenging. A recent study shows, however, that subjective PROs do correlate with traditional gold standard on a single momentary assessment (von Below et al., 2023). Furthermore, structured and explicit instructions proven to increase the correlation between PRO-items and clinical assessments, also for symptoms that are notoriously hard to self-assess, such as dyskinesia (Timpka et al., 2022; Janz et al., 2023).

Objective assessments of the listed symptoms have been developed and tested for many years, but the validation of continuous measures throughout a day against a gold standard assessment is often limited (Sica et al., 2021; Vanmechelen et al., 2022). Some IMU-based proprietary methods reported good correlations of passively generated symptom assessments and traditional gold standard assessments on larger temporal intervals (Guan et al., 2021; Rodríguez-Martín et al., 2022). However, some passive assessments correlate better with gold standards on larger rather than shorter temporal intervals (Joshi et al., 2019), where others only report their performance over larger periods of time (Powers et al., 2021). These limitations challenge the interpretation of these assessments over short time intervals. An increasing number of studies reports on the application of active, sometimes gamified, motor assessments either to assess naturalistic motor or cognitive symptoms (Adams et al., 2023; Broeder et al., 2023; Crook-Rumsey et al., 2023; Liikkanen et al., 2023), or to improve symptoms due to training exercises (Gallou-Guyot et al., 2022). They mostly report good feasibilities, some requiring remote support, good test accuracies (Broeder et al., 2023), but also remaining challenges around the interpretation (Page et al., 2022; Liikkanen et al., 2023).

Although the perception and interpretation of cardinal PD symptoms may be generalized largely over PD population globally, it is advised to test the validity of assumed relevant variables in local, independent populations before applying them in predictive modeling (Kelly et al., 2019).

Sauerbier et al. (2017) discussed a large heterogeneity in self-reporting of motor and non-motor symptoms in PD, but that mostly, reliable information on non-white patients is lacking. The FIRE-PD study supported engagement of underrepresented groups (Sanchez et al., 2022), with results not yet published. A very recent study investigated the perception of dyskinesia in different cultures and even stated possible language-based influences on self-reports vs. clinical examination (Kaasinen et al., 2023).

This underlines the importance of reassuring a specific geographical, socio-economic, or cultural PD population agrees with the validity of monitoring methods merely based on existing literature.

It is particularly important to evaluate the inclusivity of the monitoring methods for underrepresented groups among the PD population, since large studies often do not reflect the preferences of these groups (Sanchez et al., 2022).

Patient engagement in DBS: concepts and preliminary outcomes

Objectives of patient engagement

We established two primary goals for our patient engagement initiatives:

Enhanced insight: Our intention is to gain a clearer understanding of patient preferences and the potential burdens they face, whether from active participation or passive naturalistic data collection.

Comprehensive experience capture: We aim to ensure that no vital patient experiences go unnoticed. Our multifaceted monitoring methods should wholly represent patients' symptoms and overall functionality.

Accomplishing these objectives is anticipated to boost study feasibility and participant adherence, leading to superior data integrity. Here, we will now report on the methodology and the resulting consequences of patient engagement applied, briefly introducing our study design before the patient engagement as the basis for this use case.

Study design

We planned to investigate electrophysiological biomarkers in PD patients treated with bilateral subthalamic DBS in a chronic setting. To better interpret the naturalistic neural biomarkers, we ask the participants to use naturalistic monitoring methods in their real-life situation, resulting in objective and subjective measures of symptom severity and general context parallel to the neural recordings. This multi-modal, high intensity data acquisition will be applied during blocks of 2 to 4 weeks, and will be complemented with clinically validated motor and non-motor assessments during hospital visits.

For the subjective assessments, we composed an EMA questionnaire with 16 items covering motor-, non-motor-symptoms and contextual information, based on the available literature (Habets et al., 2020; Morel et al., 2023). A custom-made smartphone-application will prompt the questionnaire on six semi-random times throughout the day (VirgoBit UG, Muenster, Germany).

For the objective assessments, we provide the patients with a commercially available wearable wrist sensor (CardioWatch, Corsano B.V., The Hague, Netherlands) that records heart rate derived measures, activity proxies, sleep staging, and raw accelerometer data. To collect neurophysiological recordings, we will use a passive recording setting from a sensing-enabled internal pulse generator that records one mean value in a pre-defined frequency-bin every 10 min. Besides this passive recording, we will ask the patients to perform an active neurophysiological recording at every EMA-completion.

Methodology of patient engagement

The developed patient engagement concept covers active patient involvement throughout the whole study duration (see **Figure 1B**). First, we will consult a small group of patients during the conceptualization and design of the study. Based on availability and travel distances, we will ask some of these patients to pilot the proposed recording protocol for 2 weeks. After the piloting phase, we will again consult these patients in a group event, to collect feedback and discuss our learned lessons. During the actual study, we will continue to include a group of patients through a "patient expert advisory board." We will consult and inform this advisory body regarding practical issues and scientific progress via repetitive events. Here, we will discuss our design, preparation, and results from the initial patient engagement meeting, as well as first experiences from the second patient engagement meeting.

We invited PD patients treated with subthalamic DBS that would meet all inclusion criteria for our upcoming study. To maintain a familiar and approachable atmosphere, we made sure the group size did not exceed ten patients. We ensured to have a diverse patient subset regarding age, gender, and general technology affinity. To reduce the patient burden, we included patients with travel times less than an hour. We invited patients to bring an accompanying person of choice. Patients often brought a partner, relative, child, parent, or close friend. Finally, nine patients accepted our invitation.

The goal of the initiating meeting was to discuss feasibility of the planned study and assess unmet needs or concerns of the participants.

The agenda started with a brief update on the current state of research relevant to the planned study to bring everyone to a similar basis for discussion. Therefore, we explained current findings and challenges of biomarker research and introduced the planned selected methods in the prospective study.

After this, we had four breakout sessions with two groups, discussing with scientists and clinicians. We pre-selected four discussion topics that demanded patient and caregiver input:

- Passive and active sensor-based data collection
  - *Would wearing a wearable continuously be feasible?*
  - *Which device specifications would be important for you (recorded measures, waterproofness, recharging)?*
  - *Would self-induction of recordings with an additional device be tolerable?*
  - *Would you participate in additional measures such as a video game and what should that look like?*
  - *What would be your preference for data transfer?*
- Ecological momentary assessment
  - *Are the questions understandable, do you have doubts regarding interpretations?*
  - *Do you miss symptoms or functionality assessed?*

- *Do you think the number of items, the frequency or questionnaires, and the EMA method are feasible?*

- Study design and support
  - *Would you like a patient advisory board and what should its role be?*
  - *Do you prefer study set up meetings at home or in the hospital; would you like to bring a supporting person?*
  - *How do you prefer to communicate in case of questions during participation?*
  - *What do you think of the current user interface and the feedback it is providing?*

- Open points and further ideas
  - *Are any points/symptoms that are important for you missing?*
  - *What are your thoughts on further smartphone-based measures?*
  - *In what form would you like to receive research results?*
  - *How did you like today's meeting and would you like scientific meetings in future?*

Results and consequences of patient engagement meeting

The overall results of feedback concerning the different points are summarized in **Table 1**.

Regarding sensors, the main concern of participants was a user friendliness in the sense that it should not need recharging too frequently and should be robust enough to be worn continuously (e.g., also during showering) to avoid data loss due to damage of the sensors or forgetting to reaffix it.

Active data acquisition should be kept as simple as possible—additional devices were seen critically, but a small motor task as a game was received positively. Here, the unanimous opinion was that it should be as gamified as possible and that features like a high score would increase motivation.

When asked whether passive measures, such as typing speed, could in their opinion reliably be used instead, they preferred active measures.

Initially, patients were skeptical about the high intensity recording phases. However, they showed more confidence in these methods after highlighting the scientific value of monitoring data with high temporal resolutions for shorter periods of time (e.g., weeks) compared to only daily measures for longer periods (e.g., months).

The patients preferred very explicitly formulated EMA-items that clarified whether items focus on PD symptoms or on the general wellbeing. The use of solely Likert-scalers and multiple-choice questions was positively accepted.

Interestingly, many patients and relatives had concerns regarding personal data and data transfer. It became clear that for the matter of data security, but also for concerns of data loss, a local saving or automatic transfer to a secure local server would be preferable.

There seems to be a large demand for study support. This implies both a clinical team for medical backup, but also patient experts for representation of the patient perspective and "everyday aspects" of the data acquisition. Since there was an individual variability of preferences, it was advised to offer the study support via study phone and email. Also, there was a strong demand for being involved in the whole scientific process: scientific meetings, updating on the study progress, results and interpretation of data at regular intervals was desired.

The insights from our patient engagement session led to significant modifications in our study design. Practically speaking, even though the original application was well-received, we optimized its framework. The final version now consists of 13 questions: 1 general, 5 on motor symptoms/medication, 3 addressing non-motor symptoms, and 4 contextual inquiries. We also enhanced the application's home screen based on user feedback, displaying the previous week's participation scores, cumulative step count, and average heart rate. Additionally, we've incorporated battery life details for the wearable sensor and a recharging notification. We agreed with the patients on trying out active measures, e.g., initiation of electrophysiological recordings during the piloting phase, to test the theoretical concerns in practice.

Patients responded positively to study support via patient manuals and several communication ways (phone, email). There will be an individual setup meeting with each participant and at least one relative/caregiver. During this, we will explain the study components with different devices, questionnaires and

TABLE 1 Patient feedback on breakout-session topics.

Passive/active data collection	EMA
• As little additional devices as possible → 8/9 patients owned smartphones, 8/8 would use their own device for monitoring • Afraid to lose data, as passive data collection as possible is preferred • Active collection should be as gamified as possible, opinions on frequency vary between several times per day to weeks, event recording may be too much	• 2 weeks, multiple times per day may be feasible, if there is no pressure for continuous and complete documentation • Formulation of questions need clarification whether applying to PD-specific symptoms or general well-being vs. general. Supported question-instructions are required at study start. • Proposed user interface was okay, but adjustable font size would be desirable • Visual feedback: beyond a track record of EMA completion, biometric data like steps or heart rate would be desirable
Study support	**Additional points**
• Proactive calling/visiting is desired by most • Personal setup visit (including caregiver), good manuals for at home • Study email address and phone for contact • Patient expert panel appreciated as a "backup trust person," but a dedicated infrastructure including medical professional support would be preferred	• As little personal data as possible Global Positioning System (GPS, app usage) • Very critical about passive measures, e.g., typing speed, in this case, active engagement with e.g., games would be preferred • Regular information events/accessibility of scientific results desirable

our support structure. With structured control questions, we will assess whether patients understood the key information. Addressing feedback on individual preferences on location of the setup meeting, we give patients the possibility of an in-clinic or an at-home visit. We also agreed on a second patient engagement meeting after the piloting phase, during which feedback is assessed and a final study protocol is agreed upon (see **Figure 1B**). There, also the first results will be discussed, as will be the case in update meetings twice per year during the main study.

After a piloting phase of on average 5–7 days with five patients, we had another patient engagement consultation. Here, we received feedback regarding the feasibility of the study design. The overall design with active and passive measures was positively received, and a duration of two-weeks home monitoring was favored. The concern that these times should be planned according to participants' schedules was raised, e.g., that times with vacation should be avoided in order to capture the "everyday life." The questionnaires were experienced as not disturbing, with average completion times around < 120 s. Regarding the wearable, the most important consideration was to ensure continuous data acquisition with as little technical demands to the patients as possible. For some patients, too many parallel technical devices (e.g., if not the personal phone could be used) were considered stressful. We agreed on a procedure with the study protocol, including another brief piloting phase.

Concluding remarks

We here would like to underline the importance and scientific potential of patient engagement methods to enhance naturalistic neuromodulation research in general. More specifically, our patient engagement use case in a naturalistic monitoring study for PD DBS can help researchers to close the gap between the real-life data they desire, and the feasible data and real-life circumstances in which patients collect these data. The reported experiences while preparing, executing, and evaluating our patient engagement activity may guide colleague researchers in movement disorders and/or DBS communities that consider including patient engagement in their studies.

Due to the novelty of multi-modal naturalistic monitoring with high-resolution data collection, it was very valuable to hear patients' general perceptions of our study design in a different setting than an informed consent conversation. Our impression was that the attending patients felt free to give their honest opinion, since they were considered the "experts" throughout this whole activity.

After our patient engagement session, we revised multiple elements of our study. We pinpointed the key symptoms patients deemed vital to track. While we made subtle tweaks to the monitoring app's user interface, like font size adjustments and biomarker feedback, a standout insight was the emphasized need for a study support structure. We incorporated this, firmly believing it will be pivotal to bolster patient compliance. We generally found that the patient engagement meeting was also valuable for patient empowerment to foster study motivation and tailor a study design to individual needs. For example, the willingness for high resolution active input was increased when participants understood the scientific necessity, and also realistic burden of e.g., completing the questionnaires. With the second patient engagement meeting, we yielded valuable improvements of our study protocol for long-term feasibility of high-quality chronic data acquisition in the main study. Hence, we recommend for chronic studies to implement a multi-layered diverse patient engagement and support structure with individual and group feedback and implementation meetings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (EA2/256/60). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LF: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. JR: Conceptualization, Supervision, Writing – review & editing. AK: Resources, Supervision, Writing – review & editing. JH: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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Conflict of interest

AK declares that she was on the advisory board of Medtronic and Boston Scientific, and had received honoraria from Medtronic and Boston Scientific, LF received honoraria for talks for Medtronic; no other relationships or activities that could appear to have influenced the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Prefrontal network engagement by deep brain stimulation in limbic hubs

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Prefrontal circuits in the human brain play an important role in cognitive and affective processing. Neuromodulation therapies delivered to certain key hubs within these circuits are being used with increasing frequency to treat a host of neuropsychiatric disorders. However, the detailed neurophysiological effects of stimulation to these hubs are largely unknown. Here, we performed intracranial recordings across prefrontal networks while delivering electrical stimulation to two well-established white matter hubs involved in cognitive regulation and depression: the subcallosal cingulate (SCC) and ventral capsule/ventral striatum (VC/VS). We demonstrate a shared frontotemporal circuit consisting of the ventromedial prefrontal cortex, amygdala, and lateral orbitofrontal cortex where gamma oscillations are differentially modulated by stimulation target. Additionally, we found participant-specific responses to stimulation in the dorsal anterior cingulate cortex and demonstrate the capacity for further tuning of neural activity using current-steered stimulation. Our findings indicate a potential neurophysiological mechanism for the dissociable therapeutic effects seen across the SCC and VC/VS targets for psychiatric neuromodulation and our results lay the groundwork for personalized, network-guided neurostimulation therapy.

KEYWORDS

deep brain stimulation (DBS), major depressive disorder (MDD), ventral capsule/ventral striatum, subcallosal cingulate, gamma oscillations, prefrontal networks, stereo-EEG/intracranial recordings

1 Introduction

The ability to regulate complex emotions and make controlled decisions are central to the human experience and critical for successful navigation through challenging life circumstances. Neuroimaging and electrodiagnostic studies have implicated prefrontal networks encompassing the dorsal anterior cingulate cortex (dACC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC) and amygdala in affective and emotional regulation (Delgado et al., 2008; Etkin et al., 2011, 2015; Groenewold et al., 2013; Hiser and Koenigs, 2018), decision making and impulsivity (Elliott et al., 2000; Shenhav et al., 2013; Hiser and Koenigs, 2018), reward evaluation (Bush et al., 2002; Lipsman et al., 2014; Saez et al., 2018; Knudsen and Wallis, 2020), and emotional processing (Pessoa and Adolphs, 2010; Geissberger et al., 2020). Within electrophysiology studies spanning across species, both low and high frequency oscillations across prefrontal, limbic and cingulate structures have emerged as key signals involved in distinct aspects of cognitive, affective and reward processing. Examples of such signals include theta band (4–8 Hz) and gamma band activity (60–140) in the dACC (Rothé et al., 2011; Heilbronner and Hayden, 2016; Widge et al., 2019) for cognitive control processing and adaptation, respectively, alongside gamma activity for conflict processing in the OFC (Tang et al., 2016). Similarly, theta, beta (13–35 Hz) and gamma activity have emerged as critical neural features representing reward valuation, expectation, modulation and processing the OFC (van Wingerden et al., 2010; Sacré et al., 2016; Saez et al., 2018; Knudsen and Wallis, 2020; Amarante and Laubach, 2021). These spectral features are also modulated in the vmPFC and dACC during affective processing (Lipsman et al., 2014; Bijanzadeh et al., 2022). Of note, depending on anatomical structure and their associated role in executive, affective or reward function, some distinct spectral features have shown to be replicable across species and some studies (e.g., midfrontal and cingulate theta oscillations in cognitive control function). Disruption of neural activity in these implicated circuits is thought to lead to psychiatric disorders of mood, anxiety, and impulsivity, among other behavioral manifestations (Price and Drevets, 2010; Groenewold et al., 2013; Cheng et al., 2016; Williams, 2016; Ferri et al., 2017; Damborská et al., 2020; Rolls et al., 2020). Further, causal manipulations of networks underlying regulation of emotional and cognitive processing using electrical stimulation and lesioning have provided further evidence of the close relationship between disrupted neural circuits and behavioral symptoms in psychiatric disorders (Drevets, 2007; Wilson et al., 2014; Heilbronner et al., 2016; Schneider and Koenigs, 2017; Basu et al., 2019; Sawada et al., 2022). Neuromodulatory interventions (Mayberg et al., 2005; Scangos et al., 2021a) are often used to treat such disorders, but little is known about the human *electrophysiology* of these prefrontal regions in psychiatric disorders and how chronic neurostimulation therapies *modify* circuit dynamics underlying psychiatric symptoms. Characterizing the specific spatiotemporal prefrontal network activity implicated in affective and cognitive processing in response to therapeutic stimulation can inform stimulation paradigms on a chronic or adaptive basis and aid the prediction of an individual's response to stimulation.

Two well-characterized affective hubs previously demonstrated to be gateways to parsimoniously engage prefrontal and corticolimbic networks through invasive means (Mayberg et al., 2005; Quraan et al., 2014; Widge et al., 2019; Elias et al., 2022) are the ventral capsule/ventral striatum (VC/VS) and subcallosal cingulate (SCC). The VC/VS and SCC are thought to be hubs (Crowell et al., 2014) at the crossroads of white matter pathways hypothesized to influence executive function (Widge et al., 2019), reward processing (Rogers et al., 2004; Heldmann et al., 2012) and mood processing (Mayberg et al., 2005; Malone et al., 2009) through their connections of varying degrees to prefrontal and limbic structures (spanning the amygdala, PFC and ACC) (Haber, 2012; Heilbronner and Haber, 2014) with partial overlap (Gutman et al., 2009; Riva-Posse et al., 2014; Zhu et al., 2021). Modulation of the two targets have shown promising results in DBS studies showing improvement in symptoms of anxiety (Lipsman et al., 2013), depression (Mayberg et al., 2005; Holtzheimer et al., 2012; Ramasubbu et al., 2013), treatment-refractory anorexia nervosa (Lipsman et al., 2017), addiction (Mantione et al., 2010; Voges et al., 2013; Kuhn et al., 2014) and obsessive compulsive disorder (Smith et al., 2020; van der Vlis et al., 2021). In the clinical treatment of treatment-resistant depression (TRD) with deep brain stimulation (DBS), the VC/VS and SCC targets both showed initially promising open-label studies (Mayberg et al., 2005; Malone et al., 2009). However, these studies were followed up by controlled trials that failed to meet sufficient outcomes measures ultimately needed for regulatory use of DBS for treatment refractory depression (Dougherty et al., 2015; Holtzheimer et al., 2017). Of interest, while both targets can have an antidepressant effect, responses to stimulation across the two targets are phenotypically different, and notable qualitative differences in behavioral responses ("activating" vs. "calming") (Mayberg et al., 2005; Malone et al., 2009; Choi et al., 2015; Scangos et al., 2021b; Sheth et al., 2021) have been observed. Prefrontal targets appear to be key in driving a response from both DBS targets (Brown et al., 2020; Clark et al., 2020; Liebrand et al., 2020).

The aim of our study was to evaluate the network-level effects of acute stimulation *between* the SCC and VC/VS, two well-established targets used for psychiatric DBS therapy. We took advantage of a unique opportunity afforded through an ongoing clinical trial of DBS for TRD (NCT03437928) where we performed acute stimulation experiments using segmented DBS leads in the SCC and VC/VS with concurrent high-density intracranial recordings providing high spatiotemporal resolution of neural activity in two participants with TRD. We aimed to characterize the *differences* in neural response across prefrontal networks between the two DBS targets within and across patients with TRD. Given the phenotypic differences that are observable following stimulation of the VC/VS and SCC, and established role of low and high oscillations in the vmPFC, OFC, dACC and amygdala in neuropsychiatric disorders (Drevets, 2007; Myers-Schulz and Koenigs, 2012; Ferri et al., 2017; Rao et al., 2018; McTeague et al., 2020), we hypothesized that we would find differentiable neurophysiological responses to acute stimulation between the DBS targets in our aforementioned regions of interest (OFC, vmPFC, dACC, amygdala) that this would be unique to anatomical regions in high frequency activity (defined as 13–100 Hz for this study) or low frequency activity (defined as 1–13 Hz for our study) building on recent work implicating frequency-specific neural oscillations in

mood (Lipsman et al., 2014; Rao et al., 2018; Scangos et al., 2021a; Bijanzadeh et al., 2022). Our results lay the groundwork for a more mechanistic understanding of the effects of DBS across prefrontal circuits in psychiatric disease, and better equip us to implement optimized, network-guided neuromodulation in the future.

2 Materials and methods

2.1 Participant and study overview

Data for this study was collected from two participants (37 year old Latino male and a 57 year old Caucasian female) diagnosed with TRD. The participants were enrolled in an ongoing clinical trial (NCT 03437928) for DBS for TRD. Each participant gave fully informed consent according to study sponsor guidelines, and all procedures were approved by the local institutional review board at Baylor College of Medicine IRB (H-43036) prior to participation. The trial has enrolled more than two participants, but due to the changing nature of the goals of the study, certain aspects of the stimulation experiments have changed across participants. In particular, the stimulation paradigm (described below in section "2.3 Electrode stimulation and recording") for the first two participants changed such that the analyses described here were not possible in subsequent participants. Rather than combining heterogeneous analyses, we focused on the data from these first two participants with consistent acquired data.

Participants underwent stereotactic implantation of four DBS leads (Boston Scientific Cartesia, Marlborough, MA, USA) and 10 temporary sEEG electrodes (PMT, Chanhassen, MN, USA) based on pre-operative scans including patient-specific tractography. Post-implantation, patients underwent a 10-day intracranial monitoring period for evaluation of brain networks involved in depression. Following the intracranial monitoring period, sEEG electrodes were removed and the four DBS leads were internalized and connected to two implanted pulse generators (IPG) (Boston Scientific Gevia, Marlborough, MA, USA). Additional surgical details have been described previously (Sheth et al., 2021).

2.2 Electrode implantation

Intracranial sEEG electrodes for local field potential (LFP) recordings were implanted bilaterally across several cortical and subcortical targets based on previous work implicating their roles in mood, reward, as well as cognitive and affective processing (Miller, 2000; Etkin et al., 2015; Knudsen and Wallis, 2020; Friedman and Robbins, 2021). Regions sampled included the dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), lateral and medial orbitofrontal cortex (lOFC, mOFC), superior frontal gyrus (SFG), superior and medial temporal gyri (STG, MTG) and the amygdala (**Figure 1A**). Post-operative CT scans and pre-operative MRI scans were aligned using the Functional Magnetic Resonance Imaging for the Brain Software Library's (FMRIB's) Linear Image Registration Tool (FLIRT). Electrode coordinates were manually determined from the co-registered CT in BioImage Suite and placed into native MRI space. The reconstructed cortical surface, segmented cortical and subcortical structures and electrode coordinates were visualized using the Multi-Modal Visualization Tool (Felsenstein et al., 2019).

Both participants were implanted bilaterally with segmented DBS leads in the VC/VS and the SCC, capable of current steering. The DBS leads used in our study consist of eight stimulation contacts: solid ring contacts at the deepest and shallow positions, as well as three-way segmented contacts located between the ring contacts. Seven total contact configurations of interest were identified per lead, including three stacked configurations listed as follows: (1) anterior-facing contacts 2 and 5, (2) posterior-left facing contacts 4 and 7 and (3) posterior-right facing contacts 3 and 6. The remaining four configurations tested were ring configurations listed as follows: (1) solid ring contact 1 (2) solid ring contact 8 (3) combination of segmented ring contacts 2, 3, and 4, and (4) combination of segmented ring contacts 5, 6, and 7 (**Figure 1B**).

2.3 Electrode stimulation and recording

Monopolar cathodic stimulation was delivered through each DBS lead via a Blackrock CereStim R96 (Blackrock Microsystems, Salt Lake City, UT). A stimulation amplitude of 4.8–5 mA was delivered at the solid ring contacts, whereas for stacked or ring configurations this amplitude was split evenly among contacts to enable current steering, never exceeding 5 mA in total or at any time a charge density of 30 $\mu C/cm^2$. Stimulation was applied at 130 Hz, with a pulse width of 180 μS and interphase gap of 100 μS. In participant A, we tested the seven identified stimulation combinations (3 stacked configurations, 4 ring configurations) for each DBS lead in the SCC, and five combinations (3 stacked configurations, 2 ring configurations) in each DBS lead in the VC/VS. In participant B, we tested all seven combinations across each of the four DBS leads. Each trial of stimulation consisted of 15 s of stimulation on followed by 10 s without stimulation (**Figure 1C**). Trials were repeated 5 times per contact configuration per DBS lead seriatim, resulting in 25–35 trials per DBS lead for participant A and 35 trials per DBS lead for participant B.

2.4 Data acquisition and signal processing

Electrophysiological signals from implanted sEEG electrode contacts were recorded using a 256-channel NeuroPort Acquisition System (Blackrock Microsystems, UT, USA) at a sampling rate of 2 kHz, with a hardware high pass filter applied at 0.3 Hz. Recordings from sEEG contacts were analyzed offline using custom scripts written in MATLAB (Mathworks Inc. Natick, MA, USA) and Python. LFP signals were demeaned, decimated to 1 kHz and bandpass filtered between 1 and 250 Hz. A butterworth notch filter was applied to remove line noise at 60, 120, and 180 Hz, respectively. Recordings were bipolar re-referenced by subtracting the activity of adjacent electrode contact pairs. Any channels with excessive noise or without a clear neural signal were removed from the analysis. To evaluate the response of the sampled networks before and after stimulation, we analyzed the

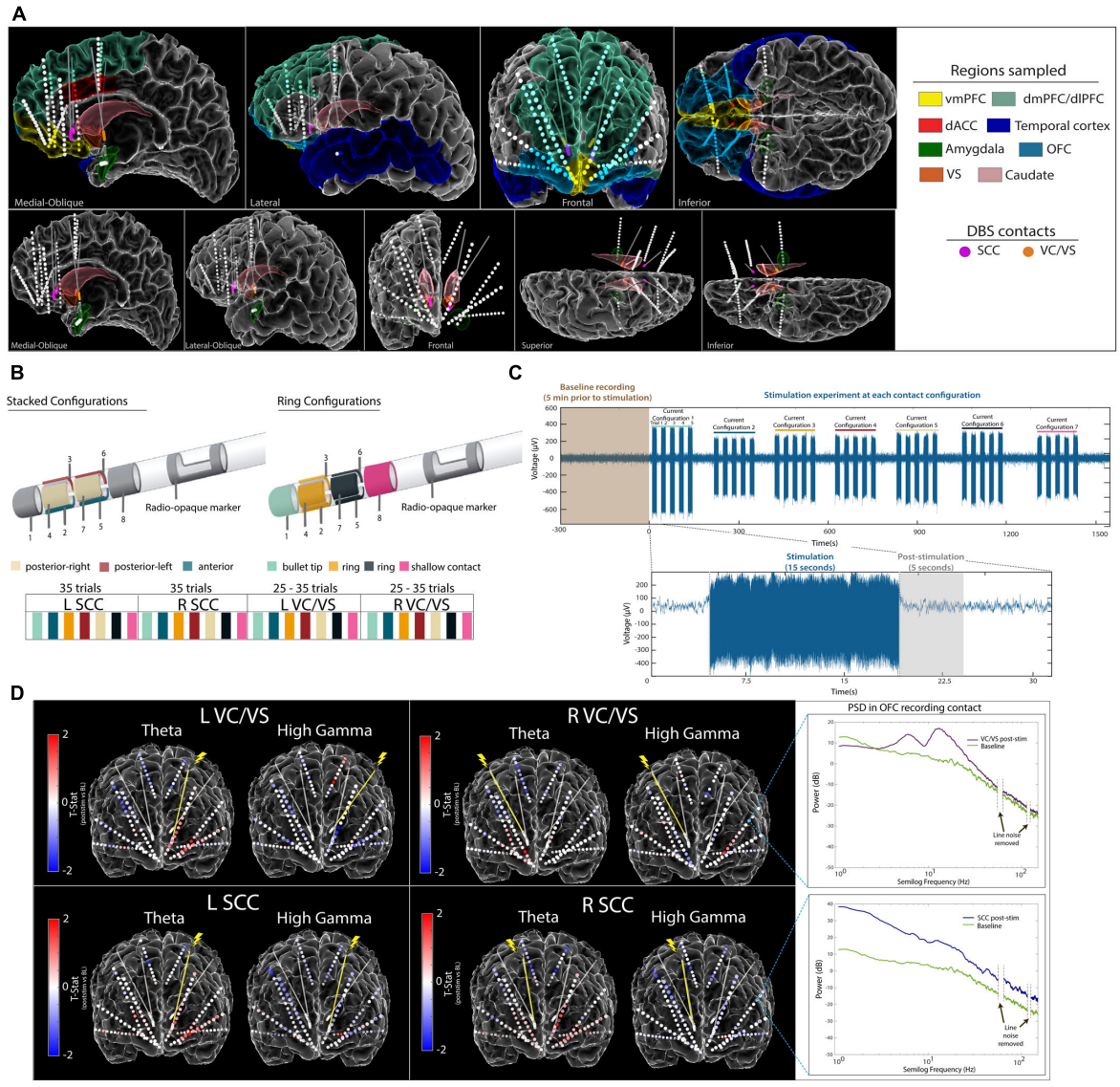

FIGURE 1
Experimental Approach. **(A)** Anatomical reconstruction showing placement of sEEG electrodes (top panel) and DBS leads (bottom panel). Colors in the legend (right) correspond to the region where electrodes were implanted. The vmPFC, OFC, dACC, and Amygdala were regions of interest for this study. **(B)** Steerable DBS leads were used to deliver unilateral stimulation in the VC/VS and SCC, respectively. Seven current configurations of interest were identified and tested across participants. **(C)** Raw voltage signal recorded on an example sEEG contact during stimulation in the left SCC DBS lead. Participants were systematically tested at each current configuration for 15 s, with five trials per current configuration at each respective DBS lead. A 5-s window following stimulation was used for subsequent analyses.**(D)** Electrode diagram showing the mean power change in theta band and high gamma band following stimulation for participant A. Each contact is colored based on the t-statistic value computed between baseline and post-stimulation for each DBS lead (red indicates increase in power following stimulation and blue indicates a decrease in power following stimulation). Inset (right) shows log-transformed power spectra from a recording electrode in the OFC during baseline and post-stimulation. vmPFC, ventromedial prefrontal cortex; lOFC, lateral orbitofrontal cortex; mOFC, medial orbitofrontal cortex; dACC, dorsal anterior cingulate cortex; VC/VS, ventral capsule/ventral striatum; SCC, subcallosal cingulate.

spectral power in the 5 s following stimulation to avoid artifact contamination. We identified a window of 600 ms post-stimulation that was additionally excluded from analysis to avoid residual post-stimulation artifacts in the signal. The multitaper spectral estimation method was used to extract power spectral density (PSD) from the sEEG recording using the *mspectrumc.m* function from the Chronux toolbox (Bokil et al., 2010). Spectral power was then averaged within standard frequency bands (delta = 1–4 Hz, theta = 4–8 Hz, alpha = 8–12 Hz, beta = 12–30 Hz, low-gamma = 30–55 Hz, high-gamma = 65–100 Hz). The spectral power across the baseline windows and post-stimulation windows across all stimulation experiments were z-scored within participants. Electrode contacts in gray matter located in the regions of interest were identified and pre-processed signals were then grouped (averaged) per region of interest. The location of electrode contacts in gray matter vs. white matter and the labels for anatomical region of interest was verified by visual review of the MRI and CT by an expert rater (BS).

Prior to starting the stimulation experiments, 5 min of baseline recording was collected for each participant (**Figure 1C**). To

avoid temporal autocorrelation, the autocorrelation was computed for spectral power within each frequency band of interest and region of interest, across time (**Supplementary Figure 2**). The number of lags t where the autocorrelation was at or below 0.1 and all subsequent autocorrelation values were between 0.1 and −0.1 was identified. Lag t was then used to generate surrogate "trials" from the baseline recording, where t seconds was skipped every 5 s. The resulting 5-s trials were used for analysis to compare against the post-stimulation windows during the stimulation experiments (additional details in **Supplementary Figure 2**).

2.5 Statistical analysis

As this study includes two participants, no conclusions about a clinical population with refractory depression can be drawn. The goal with the described analyses is to identify robust, statistically reliable patterns of stimulation-induced network response observed *within* a given participant that cannot be explained by random variation or chance. In order to carefully control for multiple comparisons as our analyses is performed to assess differences across conditions (pre- and post- stimulation, VC/VS vs. SCC stimulation) across ROIs and neural features, we performed the statistical testing procedures described below.

To test the difference between pre- (baseline) and post-stimulation, non-parametric permutation testing was performed on the z-scored data using custom scripts written in MATLAB. Data labels from post-stimulation and baseline windows were randomly shuffled, and then the absolute value of the t-statistic for a two-sample, pooled variance, t-test was computed for each pair of shuffled data. This procedure was repeated 1000 times. We used a single-step maxT procedure to correct for multiple tests (Westfall and Stanley Young, 1993; Nichols and Holmes, 2002), namely, each absolute t-statistic was compared to the distribution (over permutations) of the maximal absolute t-statistic across all regions of interest and frequency bands of interest in order to obtain corrected p-values that control the familywise error rate (corrected p-values reported in **Supplementary Tables 1–4** and uncorrected p-values are reported in **Supplementary Tables 7–10**).

To test the difference between PSD changes across the network following unilateral VC/VS stimulation vs. SCC stimulation, non-parametric permutation testing was performed on the z-scored data using custom scripts written in MATLAB. We compared the effect of unilateral VC/VS to unilateral SCC stimulation (i.e., left VC/VS was tested against left SCC stim and right VC/VS stim was tested against right SCC stim). Data labels for unilateral SCC stimulation and unilateral VC/VS stimulation were randomly shuffled, and then the absolute value of the t-statistic for a two-sample, pooled variance, t-test was computed for each pair of shuffled data. This procedure was repeated 1000 times. We used a single-step maxT procedure to correct for multiple tests (Westfall and Stanley Young, 1993; Nichols and Holmes, 2002), namely, each absolute t-statistic was compared to the distribution (over permutations) of the maximal absolute t-statistic across all regions of interest and frequency bands of interest in order to obtain corrected p-values that control the familywise error rate (corrected p-values reported in **Supplementary Tables 5**, **6** and uncorrected p-values are reported in **Supplementary Tables 11**, **12**). Additional details on statistical testing are described in the **Supplementary material**.

3 Results

The goal of our study was to quantify prefrontal network responses to intracranial stimulation between two DBS targets: the SCC and VC/VS. We first evaluated the effects of stimulation for each DBS target (pre- vs. post-stim, p-values adjusted to compensate for multiple comparisons reported in **Supplementary Methods** and **Supplementary Tables 1–4**; **Figure 1C**) on high-density stereo-EEG (sEEG recordings) in two participants with TRD (**Figures 1A, B** and **Supplementary Methods**). We then compared neural responses (see **Supplementary Methods**) following stimulation between the two DBS targets (SCC post-stim vs. VC/VS post-stim, adjusted p-values reported in **Supplementary Tables 5**, **6**) on high frequency neural activity (beta, low gamma and high gamma band power) and low frequency activity (delta, theta and alpha band power). A representative example of the electrode coverage is shown in **Figure 1D**, illustrating bilateral modulation of low frequency power (e.g., theta) and high frequency power (e.g., high gamma) across recording contacts following unilateral stimulation in participant A. Statistical limitations in our study with $N = 2$ participants preclude any conclusions about a broader clinical population. However, identifying differences across conditions *within* a participant that cannot be estimated by chance entails carefully accounting for the multiple testing problem as we have done in our statistical analyses described in the section "2 Materials and methods."

Given the previously established roles of the dACC, amygdala, OFC and vmPFC in affective and cognitive regulation in psychiatric disorders, we focused our analyses across these key four anatomical regions within each subject and describe our findings for each key region in detail below.

3.1 vmPFC

We first sought to understand the effect of stimulation on high frequency activity in the vmPFC given its broad involvement in cognitive, affective and emotional processing (Hiser and Koenigs, 2018), shown in **Figures 2A–F**. Here, we found consistent differences when evaluating neural responses in high frequency bands between SCC and VC/VS stimulation (**Figures 2C, F**) in both participants. **Specifically, we found that SCC consistently increased gamma power in both participants while VC/VS decreased gamma power.** Within Participant A, left SCC stimulation elicited a significant increase in spectral power in high gamma (pre- vs. post-stim, adj.$p < 0.01$). The response to stimulation was significantly different between both DBS targets in high gamma band (adj.$p < 0.01$) and low gamma band (adj.$p < 0.01$) irrespective of the hemisphere of stimulation. The inverse relationship in which SCC increased high-frequency activity and VC/VS decreased high-frequency activity was also observed in beta band (adj.$p < 0.001$) in participant A. In

Participant B (**Figure 2D**), we observed right VC/VS stimulation significantly decreased low gamma power (adj.p < 0.05) and beta power (adj.p < 0.001) from baseline. In the same participant, neural responses were significantly different between the two DBS targets as observed in low gamma (adj.p < 0.05) and high gamma (adj.p < 0.01; **Figure 2F**).

We next explored if the same opposing response between SCC and VC/VS was observed in low-frequency activity. We did observe a significant difference in delta power between SCC and VC/VS stimulation in both participants (**Figures 2C, F**). While both SCC and VC/VS stimulation significantly increased delta power from baseline (adj.p < 0.01), respectively, we found that VC/VS stimulation drove a larger increase in delta power than SCC stimulation and the responses between the two DBS targets were significantly different (adj.p < 0.05) in participant A. In participant B, it appears that while both SCC and VC/VS stimulation drive a decrease in delta power from baseline (**Figure 2D**), the response between the two targets is still significantly different, where VC/VS drives a smaller decrease than SCC stimulation (adj.p < 0.01; **Figure 2F**).

3.2 Amygdala

The next area of interest for this study was the amygdala (**Figures 3A–F**), given its role in emotional regulation (Pessoa and Adolphs, 2010). In the amygdala, **while both VC/VS and SCC stimulation elicited increases in low and high gamma power, responses in both low and high gamma were still significantly different between the DBS targets in both participants** (**Figures 3C, F**). SCC stimulation significantly increased high frequency activity from baseline in both participants (**Figures 3A, D**). In participant A, SCC stimulation drove a significant increase in beta (adj.p < 0.001), low gamma (adj.p < 0.001) and high gamma power (adj.p < 0.001). In participant B, right SCC stimulation significantly increased low gamma (adj.p < 0.001) and high gamma power (adj.p < 0.001) while significantly decreasing beta power (adj.p < 0.01). VC/VS stimulation also significantly increased high gamma power in both participants (adj.p < 0.05; **Figures 3A, D**). In participant A, right VC/VS stimulation also significantly increased low gamma power (adj.p < 0.05) and in participant B, left VC/VS stimulation significantly decreased beta power (adj.p < 0.05). When contrasting neural responses between the two DBS targets (**Figures 3C, F**) we observed that SCC increased low gamma (adj.p < 0.05) and high gamma power (adj.p < 0.05) significantly higher than VC/VS stimulation, and right SCC increased beta power significantly higher than VC/VS stimulation (adj.p < 0.01) in participant A. In participant B, beta power and high gamma power were again significantly higher (adj.p < 0.05) following right SCC stimulation compared to right VC/VS stimulation, and low gamma power was significantly higher (adj.p < 0.001) following SCC stimulation compared to VC/VS stimulation irrespective of the hemisphere of stimulation.

Across low frequency bands, we found responses to SCC and VC/VS stimulation were significantly different in theta band in participant B (adj.p < 0.01; **Figures 3C, F**). Here, SCC drove a decrease in power relative to the VC/VS. However, no consistent modulation of low frequency activity across the two participants was otherwise observed.

3.3 Lateral and medial OFC

The lOFC was a third target of interest because it has been implicated in cognitive and reward processing and recently employed as a target for neuromodulation to improve mood (Rao et al., 2018; Scangos et al., 2021b). Results to stimulation between DBS targets are shown in **Figures 4A–F**. We found neural responses to SCC stimulation were significantly different from VC/VS stimulation in participant A (adj.p < 0.05; **Figure 4C**) and once again followed the same inverse relationship seen in the amygdala, **where SCC drove an increase in power in beta, low gamma, and high gamma bands relative to the VC/VS.** In the same participant, SCC stimulation also significantly increased beta, low gamma and high gamma power from baseline (adj.p < 0.01). In participant B, the significant difference in response between SCC and VC/VS stimulation was observed in high gamma power (adj.p < 0.01; **Figure 4F**) following stimulation in the left hemisphere. Surprisingly, we did not find many differences in neural responses to SCC and VC/VS stimulation across lower frequency bands. Delta band power was significantly modulated, (adj.p < 0.01): right VC/VS stimulation increased delta power and right SCC stimulation decreased delta power. The differential delta band power change was, however, participant specific.

We explored stimulation response in the mOFC separately as the lateral and medial orbitofrontal structures have shown to have distinct roles in cognitive and reward processing (Elliott et al., 2000). In the mOFC (**Figures 4G–L**), we found that differences between responses in high frequency activity following SCC vs. VC/VS stimulation were participant specific in the mOFC (**Figures 4I, L**). For example, the inverse relationship where SCC increases high frequency activity and VC/VS decreases high frequency activity was observed in participant A. Here, right SCC stimulation significantly increased beta power from baseline (adj.p < 0.001; **Figure 4G**), and we observed a significant difference in response to stimulation in beta power between the SCC and the VC/VS (adj.p < 0.01, **Figure 4I**). In participant B, SCC significantly increased high gamma power from baseline (adj.p < 0.05; **Figure 4J**). The inverse relationship between SCC and VC/VS stimulation-induced responses of high frequency activity was observed in low gamma (adj.p < 0.05) and high gamma (adj.p < 0.01), where SCC stimulation increased activity relative to VC/VS stimulation (**Figure 4L**).

When assessing stimulation response in low frequency activity in the mOFC, we found significant differences between responses to VC/VS vs. SCC stimulation seen across both participants in delta band (**Figures 4I, L**). In participant A, left VC/VS stimulation significantly increased power in delta band, and this response was significantly higher than the neural response following SCC stimulation (adj.p < 0.05). In participant B, right VC/VS stimulation significantly increased delta power relative to SCC stimulation (adj.p < 0.01).

3.4 dACC

A key region known to play an important role in cognitive control and emotional processing is the dACC (Shenhav et al., 2013; Etkin et al., 2015). In the dACC (**Figures 5A–F**), when examining high frequency activity, we found that significant

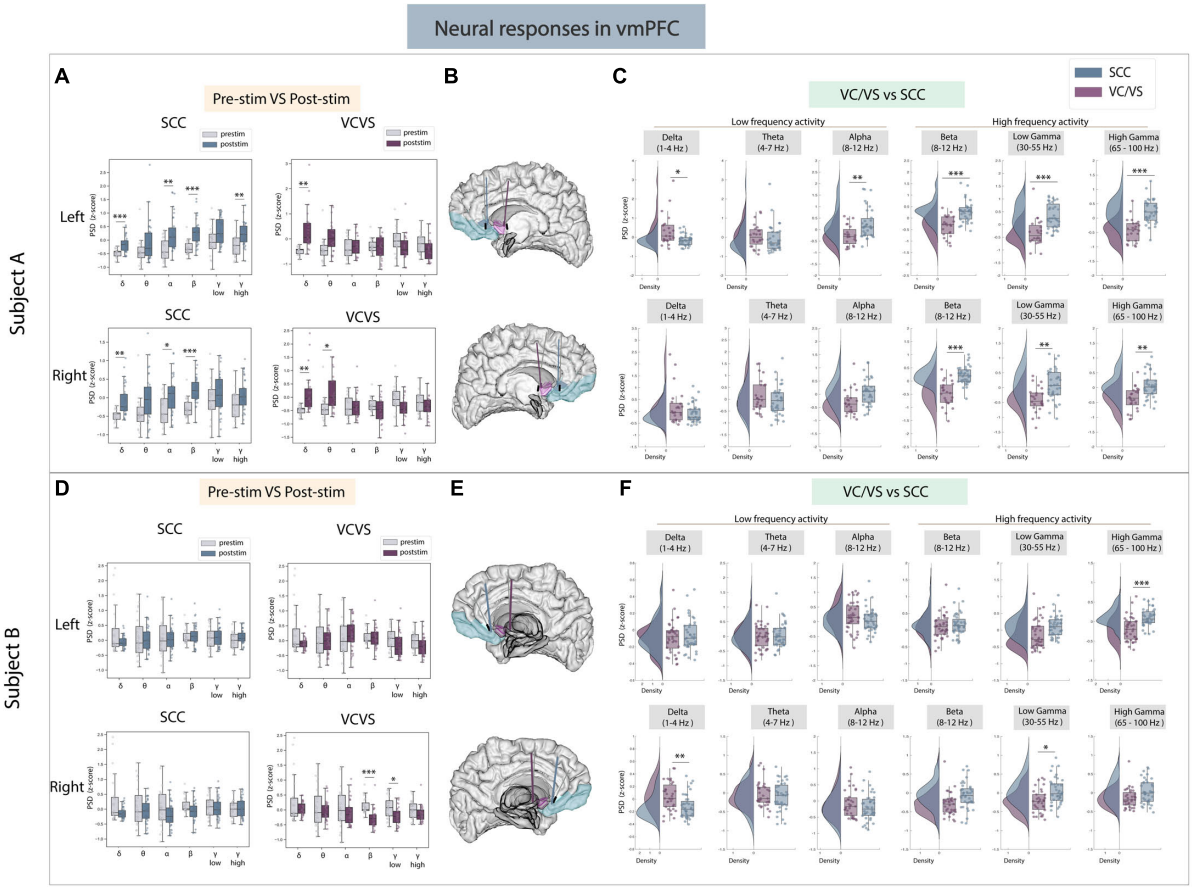

FIGURE 2
Neural responses in the vmPFC following SCC stimulation vs. VC/VS stimulation. **(A)** Distribution of spectral power across all post-stimulation trials vs. pre-stimulation (baseline) in the vmPFC after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma, and high gamma) following SCC stimulation (left) and VC/VS stimulation (right) in participant A **(B)** Corresponding anatomical location of the vmPFC highlighted in light blue and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. **(C)** Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. **(D–F)** Replicate of figures in panels **(A–C)** for participant B. *Indicates significance where adj.p-value < 0.05, corrected; **Indicates significance where adj.p-value ≤ 0.01, corrected; ***Indicates significance, where adj.p-value ≤ 0.001, corrected.

differences following stimulation between the SCC and VC/VS were also individual-specific in the dACC but still followed the inverse relationship between the two DBS targets observed in high frequency activity in other ROIs (**Figures 5C, F**). Right SCC stimulation significantly increased beta power (adj.$p < 0.01$) compared to VC/VS stimulation in participant A. In participant B, left SCC stimulation significantly increased low gamma power from baseline (adj.$p < 0.01$) while stimulation of either hemisphere in the SCC increased high gamma power (adj.$p < 0.001$; **Figure 5D**). Left VC/VS stimulation similarly significantly increased low gamma power (adj.$p < 0.05$) while stimulation of either hemisphere significantly increased high gamma power from baseline (adj.$p < 0.01$; **Figure 5D**). However, the responses between left SCC and left VC/VS stimulation were still significantly different in low gamma band (adj.$p < 0.01$; **Figure 5F**) and SCC stimulation drove a larger increase in low gamma power relative to the VC/VS.

When examining low frequency activity in response to stimulation in the dACC, we also observed a significant difference between VC/VS and SCC stimulation in delta power (adj.$p < 0.001$) in participant B–similar to the pattern observed in other ROIs–where SCC decreased power in a low frequency band (delta) and VC/VS stimulation increased power. In participant A, right SCC stimulation significantly decreased delta power (adj.$p < 0.05$) but no significant difference was observed between SCC and VC/VS stimulation in delta power.

4 Discussion

Through a unique intracranial stimulation and recording dataset collected in two participants with TRD, we obtained results with two main conclusions (**Figure 6**). First, we demonstrate that two canonical targets for psychiatric neuromodulation, the SCC and VC/VS, elicit network-wide neurophysiological responses in both high and low frequency activity following stimulation. Second, as hypothesized, we show that stimulation in the SCC and VC/VS drive differentiable neural responses. Specifically, we observed opposite effects on gamma activity in the vmPFC, and

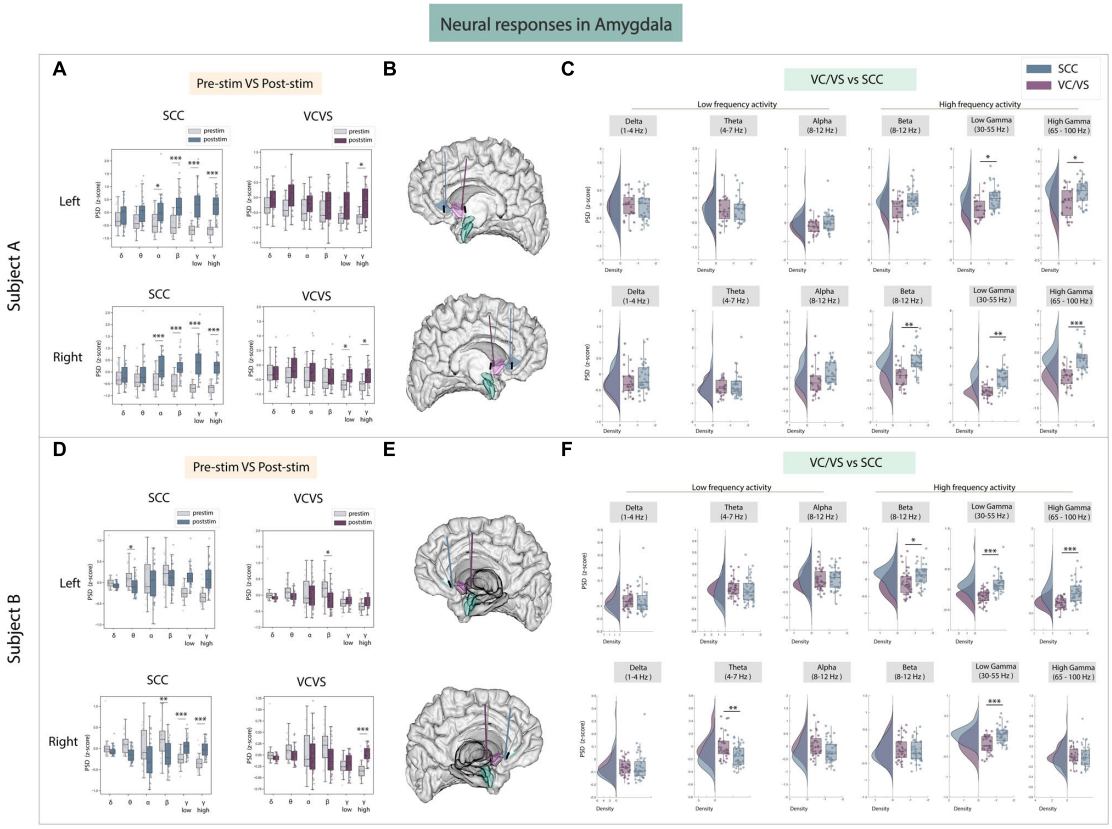

FIGURE 3
Neural responses in the amygdala following SCC stimulation vs. VC/VS stimulation. **(A)** Distribution of spectral power across all post-stimulation trials vs. pre-stimulation (baseline) in the amygdala after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma, and high gamma) following SCC stimulation (left) and VC/VS stimulation (right) in participant A **(B)** Corresponding anatomical location of the amygdala highlighted in green and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. **(C)** Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. **(D–F)** Replicate of figures in panels **(A–C)** for participant B. *Indicates significance where adj.p-value < 0.05, corrected; **Indicates significance where adj.p-value ≤ 0.01, corrected; ***Indicates significance, where adj.p-value ≤ 0.001, corrected.

differing degrees of modulation on gamma activity in the lOFC and amygdala, where SCC stimulation consistently drives a greater increase in gamma oscillations relative to the VC/VS.

Previous tractography work demonstrates that projections from the SCC and VC/VS overlap in the amygdala and medial PFC, but the anatomical trajectory and pattern of connectivity of these projections are distinct (Gutman et al., 2009; Zhu et al., 2021), including the sub-regions that receive projections from the SCC and VC/VS, respectively (Zhu et al., 2021). The difference in connectivity patterns may partially account for the distinct patterns of gamma activity in the vmPFC and amygdala between the two stimulation targets. The modulation of gamma activity seen in the amygdala is additionally supported by a recent study implementing amygdala gamma power as a biomarker for closed-loop VC/VS DBS in a case study for TRD (Scangos et al., 2021a). Interestingly, our results also show modulation of gamma activity in the amygdala following stimulation in *both* targets, but to differing degrees.

Previous studies have also demonstrated anatomical connectivity between the SCC and the OFC, and the VC/VS and the OFC (Johansen-Berg et al., 2008; Haber, 2016), and initial results from our group have shown differing effective connectivity between the SCC and VC/VS to the lOFC, respectively, in TRD participants (Adkinson et al., 2022), leading us to expect differences in neural responses between VC/VS and SCC stimulation. While we observed differing degrees of gamma power modulation in the lOFC depending on the DBS target stimulation in both participants, we did not always observe an overlap in neural responses to stimulation between lOFC and mOFC which might be explained in part by previous work indicating the distinct roles of the lateral vs. medial OFC (Cheng et al., 2016; Rao et al., 2018).

While both VC/VS and SCC stimulation can ameliorate depressive symptoms, they have been described to modulate different dimensions of affective processing and mood: VC/VS stimulation has been reported to increase motivation and energy (Malone et al., 2009; Gibson et al., 2017), while SCC stimulation has reportedly increased calmness, alertness and exteroceptive awareness (Choi et al., 2015; Riva-Posse et al., 2019). It is possible that the dissociable increase/decrease in gamma activity in the vmPFC and the differing degree of gamma modulation in the amygdala and lOFC may be underlying the differences in SCC vs. VC/VS stimulation described in acute behavioral reports seen

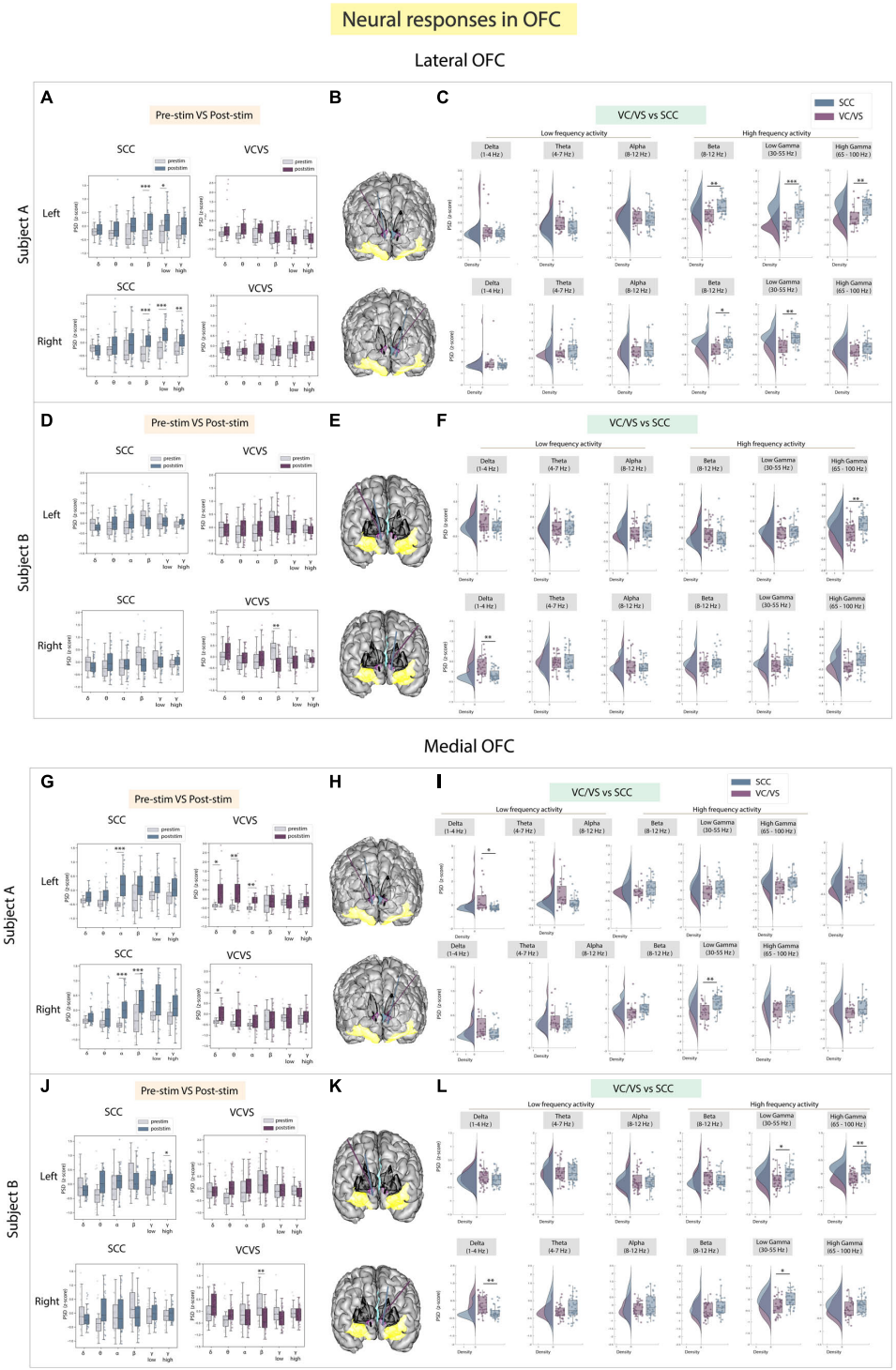

FIGURE 4
Neural responses in the OFC following SCC stimulation vs. VC/VS stimulation. **(A)** Distribution of spectral power across all post-stimulation trials vs. pre-stimulation (baseline) in the lOFC after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma, and high gamma) following SCC stimulation (left) and VC/VS stimulation (right) in participant A **(B)** Corresponding anatomical location of OFC highlighted in yellow and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. **(C)** Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. **(D–F)** Replicate of figures in panels **(A–C)** for participant B. **(G)** Distribution of spectral power across all post-stimulation trials vs. pre-stimulation (baseline) in the mOFC after z-scoring in six pre-defined frequency bands following SCC stimulation (left) and VC/VS stimulation (right) in participant A. **(H)** Corresponding anatomical location of OFC highlighted in yellow and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. **(I)** Distribution of spectral power across six pre-defined frequency bands contrasting neural responses following SCC stimulation and VC/VS stimulation. **(J–L)** Replicate of figures in panels **(G–I)** for participant B. *Indicates significance where adj.p-value < 0.05, corrected; **Indicates significance where adj.p-value ≤ 0.01, corrected; ***Indicates significance, where adj.p-value ≤ 0.001, corrected.

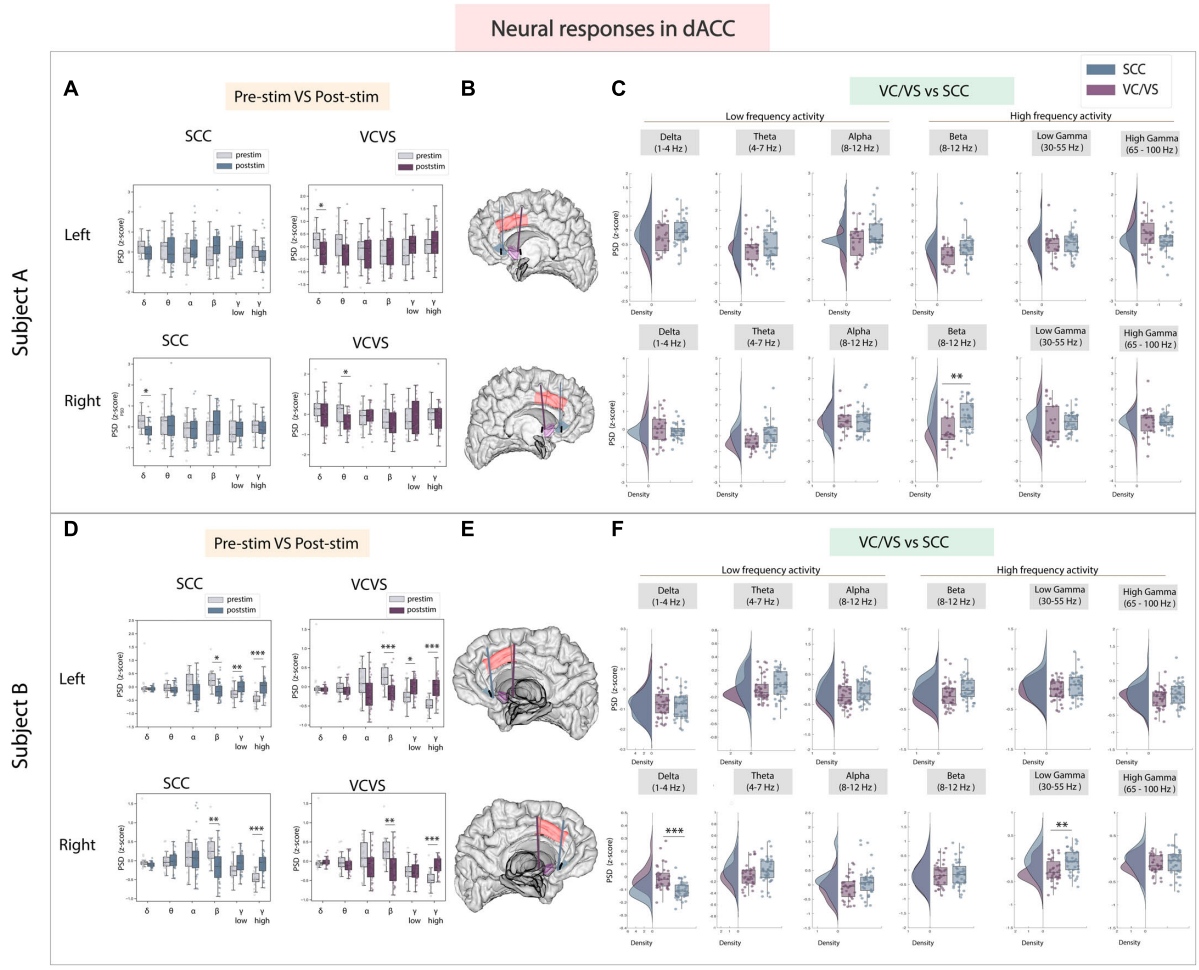

FIGURE 5
Neural responses in the dACC following SCC stimulation vs. VC/VS stimulation. **(A)** Distribution of spectral power across all post-stimulation trials vs. pre-stimulation (baseline) in the dACC after z-scoring in six pre-defined frequency bands (delta, theta, alpha, beta, low gamma, and high gamma) following SCC stimulation (left) and VC/VS stimulation (right) in participant A **(B)** Corresponding anatomical location of dACC highlighted in red and corresponding VC/VS and SCC DBS leads highlighted depending on hemisphere of stimulation. Stimulation in left hemisphere is on top, while stimulation in right hemisphere is shown on the bottom. **(C)** Distribution of spectral power across six pre-defined frequency bands comparing neural responses between SCC stimulation and VC/VS stimulation. **(D–F)** Replicate of figures in panels **(A–C)** for participant B. *Indicates significance where adj.p-value < 0.05, corrected; **Indicates significance where adj.p-value ≤ 0.01, corrected; ***Indicates significance, where adj.p-value ≤ 0.001, corrected.

elsewhere and further work will elucidate our understanding of this phenomenon.

In the dACC, we expected consistent differences in gamma power modulation following SCC and VC/VS stimulation, given recent work implicating dACC gamma power in positive affective behaviors (Bijanzadeh et al., 2022) and differential connectivity of the dACC to the VC/VS (Haber, 2016; Baldermann et al., 2021) and SCC (Johansen-Berg et al., 2008). However, differences in gamma responses between SCC and VC/VS stimulation were participant-specific. Additionally, within a given DBS lead, we observed participant-specific responses between post-stim and pre-stim in the dACC, as well as all other ROIs. The observed participant-specific stimulation responses both between and within the VC/VS and SCC suggest that increasing efforts to personalize therapy may rely on these within-participant electrophysiological signatures across networks to deliver optimized stimulation. Efforts utilizing participant-specific biomarkers for psychiatric DBS have been recently successfully demonstrated (Scangos et al., 2021a), alongside network-guided neuromodulation for psychiatric disorders (Cole et al., 2022).

Future efforts incorporating behavioral measures corresponding to functional domains within mental illness, alongside electrophysiological measurements to build brain-behavior relationships with stimulation will help identify generalizable principles that can be potentially extended to sub-domains of MDD in the broader population (Allawala et al., 2021). **Even in the absence of behavioral measurements, characterization of stimulation-induced neural response during resting state, especially between DBS targets, enables tailoring of therapy (i.e., selecting an optimal DBS target and stimulation paradigm) for disorders such as depression, based on a patient's neural response to stimulation, putative neural biomarker of mood, or another functional domain.** Our study methods currently largely operate as a research

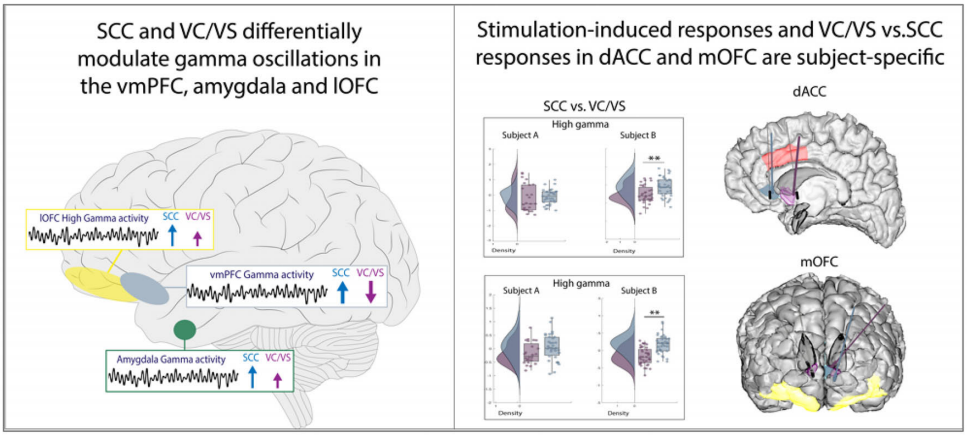

FIGURE 6
Summary of results.

tool, and while subject-specific differences are observable, it is surmisable that a greater level of consistency is achievable across a larger cohort of participants as we build on a higher sample size to quantify and model network responses to stimulation, and improve our understanding of biomarkers of symptoms in TRD. For example, as more established neural biomarkers of symptom severity (Xiao et al., 2023) or dysfunctional affective or cognitive processing in patients with TRD are uncovered, some degree of personalization and optimization would be feasible with stimulation across the VC/VS and SCC DBS targets. Indeed, efforts utilizing biomarkers to understand optimal intervention have been recently successfully demonstrated (Alagapan et al., 2023), and network-guided neuromodulation to treat psychiatric disorders has gained traction in recent years. An example of the latter is intermittent theta-burst TMS to treat depression, which currently utilizes resting state functional connectivity between the neuromodulation target of interest for TMS (dlPFC) and the SCC (an extant DBS target) to determine the sub-region for stimulation targeting (Cole et al., 2022), and to predict treatment response outcomes with TMS in the field of non-invasive neuromodulation.

Current-steered DBS provides an added parameter for differentially modulating implicated networks and neural biomarkers. A finer grained approach to precisely target anatomical regions implicated in psychopathology of depression for a desired behavioral responses is needed (Figee et al., 2022), and the degree of stimulation-induced neural response may plausibly determine a patient's therapeutic response. Future work with a larger number of stimulation trials and participants is needed to understand the extent of the effect that directionality may have on connectivity across prefrontal and limbic networks.

Primary limitations of this study include the small sample size ($N = 2$), and lack of randomization of stimulation conditions within or across the two DBS targets. While a rigorous pipeline for optimal surgical targeting was implemented (Sheth et al., 2021), one possible reason for inconsistent results within and across participants is that small variations in targeting may result in modifications in the electrophysiological effects observed. As we were concerned about insufficient time for stimulation washout between trials and stimulation parameters, the baseline window used for analysis was a 5-min recording collected prior to stimulation experiments. To address possible temporal autocorrelation in the baseline recording, we performed a correction procedure (**Supplementary Figure 2**). However, delta power in vmPFC and lOFC in Participant B had a larger amount of autocorrelation during the baseline recording that could not be fully corrected with our approach, thus, results for those specific neural features must be viewed provisionally.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Baylor College of Medicine Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review and editing, Software, Validation. KB: Data curation, Supervision, Writing – review and editing. DO: Resources, Writing – review and editing, Data curation, Investigation, Software. RM: Visualization, Writing – review and editing, Data curation. JA: Data curation, Writing – review and editing. VP: Writing – review and editing, Data curation. BS: Writing – review and editing, Data curation, Resources. MR: Data curation, Writing – review and editing, Software. SM: Writing – review

and editing, Supervision. MH: Writing – review and editing, Supervision, Formal analysis, Methodology, Validation. WG: Writing – review and editing, Supervision, Funding acquisition. NP: Investigation, Resources, Writing – review and editing, Writing – original draft, Funding acquisition, Methodology, Project administration, Supervision. SS: Data curation, Resources, Writing – review and editing, Conceptualization, Funding acquisition, Investigation, Supervision, Visualization, Writing – original draft, Methodology, Project administration. DB: Funding acquisition, Methodology, Supervision, Visualization, Writing – original draft, Writing – review and editing, Investigation.

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Conflict of interest

SS has consulting agreements with Boston Scientific, Neuropace, Abbott, and Zimmer Biomet, Varian Medical and Sensoria Therapeutics and is a co-founder for Motif Neurotech. NP was a consultant for Second Sight Medical Products, Abbott Laboratories, Boston Scientific, and Sensoria Therapeutics. WG has received donated devices from Medtronic, has consulted for Biohaven Pharmaceuticals and receives royalties from Nview, LLC. SM was supported through the use of resources and facilities at the Michael E. Debakey VA Medical Center, Houston, Texas and receives support from The Menninger Clinic. SM has served as a consultant to Allergan, Alkermes, Axsome Therapeutics, BioXcel Therapeutics, Clexio Biosciences, COMPASS Pathways, Eleusis, Engrail Therapeutics, Greenwich Biosciences, Intra-Cellular Therapies, Janssen, Levo Therapeutics, Perception Neurosciences, Praxis Precision Medicines, Neumora, Neurocrine, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, and Sunovion. He has received research support from Biohaven Pharmaceuticals, Boehringer-Ingelheim, Janssen, Merck, Sage Therapeutics, and VistaGen Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

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Cognitive outcomes in patients with essential tremor treated with deep brain stimulation: a systematic review

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Introduction: Essential tremor (ET) is a common neurological disease. Deep brain stimulation (DBS) to the thalamic ventral intermediate nucleus (VIM) or the adjacent structures, such as caudal zona incerta/ posterior subthalamic area (cZi/PSA), can be effective in treating medication refractory tremor. However, it is not clear whether DBS can cause cognitive changes, in which domain, and to what extent if so.

Methods: We systematically searched PubMed and the Web of Science for available publications reporting on cognitive outcomes in patients with ET who underwent DBS following the PICO (population, intervention, comparators, and outcomes) concept. The PRISMA guideline for systematic reviews was applied.

Results: Twenty relevant articles were finally identified and included for review, thirteen of which were prospective (one also randomized) studies and seven were retrospective. Cognitive outcomes included attention, memory, executive function, language, visuospatial function, and mood-related variables. VIM and cZi/PSA DBS were generally well tolerated, although verbal fluency and language production were affected in some patients. Additionally, left-sided VIM DBS was associated with negative effects on verbal abstraction, word recall, and verbal memory performance in some patients.

Conclusion: Significant cognitive decline after VIM or cZi/PSA DBS in ET patients appears to be rare. Future prospective randomized controlled trials are needed to meticulously study the effect of the location, laterality, and stimulation parameters of the active contacts on cognitive outcomes while considering possible medication change post-DBS, timing, standard neuropsychological battery, practice effects, the timing of assessment, and effect size as potential confounders.

KEYWORDS

essential tremor, deep brain stimulation, cognitive function, speech, VIM, cZi, PSA, review

Introduction

Essential tremor (ET) is one of the most common neurological diseases, with an estimated global prevalence of about 25 million in 2020 (Louis and Ferreira, 2010; Song et al., 2021). Medical treatment, including propranolol, primidone, and topiramate, has been shown to improve tremor severity by approximately 50% (Deuschl et al., 2011; Hopfner and Deuschl, 2020). For patients with medically refractory symptoms, deep brain stimulation (DBS) has been well-accepted as an efficacious treatment alternative with a higher efficacy (Deuschl et al., 2011).

Historically, the ventral intermediate nucleus of the thalamus (VIM) has been the main target of DBS in treating ET (Benabid et al., 1991; Sydow et al., 2003; Wharen et al., 2017). More recently, it has become evident that stimulating the adjacent areas of the VIM, such as the ventral border of the VIM or the ventrolateral or posterior (VL/VLp) thalamus or beneath in an area referred to as the posterior subthalamic area (PSA), which includes the zona incerta (Zi, caudal and rostral, or cZi and rZi) and prelemniscal radiation, is equally effective or could be more efficient with less stimulating energy needed and less stimulating related side effects in treating patients with ET and other tremors (Herzog et al., 2007; Barbe et al., 2011, 2018; Sandvik et al., 2012; Xie et al., 2012; Pedrosa et al., 2014; Ramirez-Zamora et al., 2016; Blomstedt et al., 2018; Al-Fatly et al., 2019). Stimulation within the PSA/cZi is proposed to take advantage of the small anatomical area where a large proportion of cerebellothalamic afferents can be targeted before the fibers spread out to enter the VIM nucleus (Herzog et al., 2007; Xie et al., 2012; Ramirez-Zamora et al., 2016), and also could be due to its proximity to the dentatorubrothalamic tract (Dembek et al., 2020).

DBS is an invasive procedure with multiple risks ranging from stimulation-related side effects to surgical and equipment failure-related complications (Della Flora et al., 2010). Cognitive changes have been reported as a side effect of DBS in some cases, largely depending on the DBS targets and disease mechanism (Cernera et al., 2019). The cognitive side effects of DBS in patients with ET have not been well studied due to the limited cases available, even in the most recent review (Cernera et al., 2019). As new studies and trials are emerging, here we have systematically reviewed the up-to-date literature in search of studies reporting on cognitive outcomes in patients with ET who underwent DBS targeting the VIM and its adjacent structures.

Methods

We systematically searched PubMed and the Web of Science in March 2023 for all available publications in English by keywords following PICO concepts: population (patients with essential tremor or ET), intervention (DBS or deep brain stimulation), comparators [DBS targets (VIM, VL/VLp, PSA/cZi), pre-/post-DBS, DBS settings (ON/OFF, location and laterality of the active contact, amplitude of voltage or current, pulse width, and stimulation frequency), medication state (with/without changes after DBS procedure or during the ON/OFF assessment), age at onset of ET, DBS durations at the assessment, other non-ET groups of healthy controls (HCs) or other neurological disorders with DBS as comparisons within the studies mainly for ET, and types of study designs (retrospective vs. prospective and open vs. blind)], and outcomes (neuropsychological outcomes, including mood related variables). We followed the PRISMA guideline for systematic reviews, with the flow chart of the literature search and selection process of the review being depicted in Figure 1. A total of 73 publications were found in PubMed and 194 from Web of Science as of March 2023. After removing the duplicate entries, screening was performed to narrow the publications down to 37, excluding reviews, comments, viewpoints, author responses, letters, book chapters, single case reports with insufficient information, and meeting abstracts. Then the full texts were assessed, and we further removed studies without clear outcome measures on cognitive function. We finally identified 20 relevant articles.

Results

Each of the twenty articles is listed in detail in Supplementary Table S1, with information on the disease status [e.g., ET, Parkinson's disease (PD), multiple sclerosis (MS)] and HC, DBS targets, and laterality, basic demographics, study design, DBS settings, medication status (e.g., before and after the DBS device implantation, and/or during the OFF/ON DBS assessment), and neuropsychological findings (including mood related variables). Thirteen articles were prospective design studies (Tröster et al., 1999; Fields et al., 2003; Loher et al., 2003; Woods et al., 2003; Burdick et al., 2011; Fytagoridis et al., 2013; Heber et al., 2013; Pedrosa et al., 2014; Ehlen et al., 2016, 2017; Klein et al., 2017; Philipson et al., 2019; Wang et al., 2020), with one of them a prospective randomized controlled study (Pedrosa et al., 2014). Seven articles utilized a retrospective design (Ehlen et al., 2014; Krugel et al., 2014; Jones et al., 2020; Dhima et al., 2021; Tiedt et al., 2021; Wang et al., 2021; Kielb et al., 2022).

Ten studies reported cognitive outcomes of patients following VIM-DBS for ET (Tröster et al., 1999; Fields et al., 2003; Woods et al., 2003; Ehlen et al., 2016; Klein et al., 2017; Jones et al., 2020; Wang et al., 2020, 2021; Dhima et al., 2021; Kielb et al., 2022), two studies following cZi DBS (Fytagoridis et al., 2013; Philipson et al., 2019), and two following VL/VLp DBS (Heber et al., 2013; Pedrosa et al., 2014). Six studies were compared, four of them compared VIM DBS in patients with ET with STN/GPi-DBS in patients with PD and HCs (Burdick et al., 2011; Ehlen et al., 2014; Krugel et al., 2014; Tiedt et al., 2021), one compared ET patients with VIM DBS to HCs (Ehlen et al., 2017) and one compared VIM DBS to treat tremors in patients with ET, PD, and MS (Loher et al., 2003). Thirteen studies compared cognitive outcomes pre- to post-DBS (Tröster et al., 1999; Fields et al., 2003; Woods et al., 2003; Burdick et al., 2011; Fytagoridis et al., 2013; Heber et al., 2013; Klein et al., 2017; Philipson et al., 2019; Jones et al., 2020; Wang et al., 2020, 2021; Dhima et al., 2021; Kielb et al., 2022), and nine compared cognition at DBS ON to OFF status (Loher et al., 2003; Fytagoridis et al., 2013; Heber et al., 2013; Ehlen et al., 2014, 2016, 2017; Krugel et al., 2014; Pedrosa et al., 2014; Tiedt et al., 2021). Seven studies included unilateral DBS (Tröster et al., 1999; Fields et al., 2003; Loher et al., 2003; Woods et al., 2003; Burdick et al., 2011; Ehlen

Abbreviations: DBS, Deep brain stimulation; ET, Essential tremor; VIM, Ventral intermediate nucleus; cZi/PSA, Caudal zona incerta/ posterior subthalamic area; VL/VLp, Ventrolateral or ventrolateral posterior; Amp, Amplitude; PW, Pulse width; Hz, Hertz; V, Volts; μs, Microseconds; TEED, Total electrical energy delivered.

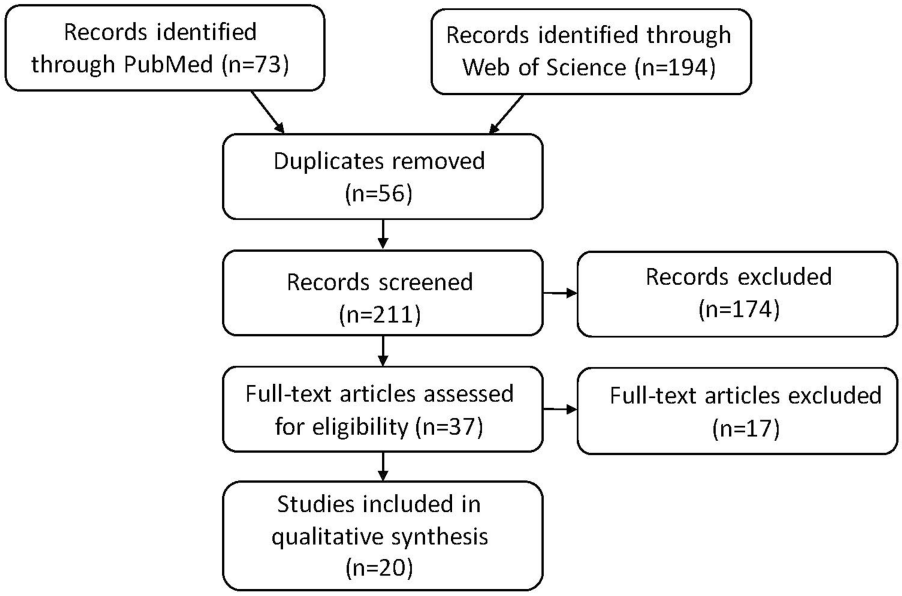

FIGURE 1
PRISMA flow diagram: literature search and selection with numbers of articles at each stage.

et al., 2014; Kielb et al., 2022), five included bilateral DBS (Krugel et al., 2014; Pedrosa et al., 2014; Ehlen et al., 2017; Klein et al., 2017; Wang et al., 2020) and eight included a mixture of patients with both unilateral and bilateral DBS (Fytagoridis et al., 2013; Heber et al., 2013; Ehlen et al., 2016; Philipson et al., 2019; Jones et al., 2020; Dhima et al., 2021; Tiedt et al., 2021; Wang et al., 2021). We summarized the findings from these studies below, with details in Supplementary Table S1.

VIM (and VL/VLp) DBS

The earliest study on cognitive outcomes in patients with VIM-DBS for ET was a prospective study of 40 patients with unilateral VIM-DBS (Tröster et al., 1999). Using a comprehensive battery of cognitive tests, this study found that 3 months after the VIM DBS, patients demonstrated statistically significant and clinically modest improvement in the cognitive domains of attention, memory, and visuospatial function as compared to 1 month prior to DBS surgery. A follow-up study 12 months post-DBS continued to show statistically significant improvements in a cognitive screening measure and tasks of fine visuomotor coordination, visuoperceptual gestalt formation, and verbal memory (Fields et al., 2003). No group-wise declines in cognition were observed, but more patients showed declines than improvements on language and visual memory tests. There were minimal changes in ET medications at 3- and 12 months post-DBS.

Another early study in 2003 was conducted on 49 patients with unilateral VIM DBS for ET and showed that 55% of patients demonstrated mild cognitive decrement (Woods et al., 2003). It was found that the group of patients with a cognitive decrement had significantly higher pulse width (>120 μs), and were more likely to have undergone left (dominant hemisphere) DBS. This study did not report on the specific cognitive domains that were affected, on the reasons for higher pulse width used, or its relationship to precise electrode location in the VIM, but the authors reported controlling for medication changes. In a study of 9 patients with ET, PD, or MS, left-sided VIM stimulation was associated with impairment in short-delayed word recall (Loher et al., 2003). The effect of laterality was further investigated in a retrospective analysis of 50 ET patients, with 14 of them on bilateral, and 36 on unilateral VIM DBS (Dhima et al., 2021). Individual-level analysis showed that 46% of patients experienced a subtle decline in overall cognition pre- and post-DBS, which correlated with higher right-sided stimulation amplitude, as did worsened visuospatial judgment. On the other hand, the longer left-sided pulse width was correlated with a decline in verbal memory performance, and higher left-sided stimulation frequency was correlated with increased perseveration during novel problem-solving. Notably, in this study, there was no group-level cognitive decline pre- and post-DBS. Additionally, medications were decreased in 46% of patients post-DBS without any benefit on cognitive outcomes in a *post-hoc* analysis.

Following the first study that reported a decline in verbal fluency in ET patients who underwent thalamic DBS (Fields et al., 2003), a handful of studies took a closer look at language outcomes. Wang et al. (2021) analyzed language-related outcomes in relationship to stimulation side and location pre- and post-DBS and found that changes in verbal abstraction had a significant correlation with stimulation location along the anterior–posterior axis within the left VIM. Patients with left ventral anterior-ventral lateral anterior (VA-VLa) nucleus activation performed worse after surgery, whereas those without the left VA-VLa activation showed significantly better performance after surgery, without medication changes pre- and post-DBS in this study. In the only prospective double-blinded randomized trial found in this review, high frequency (120–150 Hz) thalamic VLp stimulation, or areas directly beneath, reduced tremor in patients with ET but worsened verbal fluency (both semantic and phonemic) when compared to low frequency (10 Hz) stimulation and

DBS OFF (Pedrosa et al., 2014), while working memory and executive function remained unchanged between groups.

A retrospective study assessed verbal fluency in 13 ET patients with unilateral VIM DBS and 14 PD patients with unilateral STN DBS, in DBS ON and OFF states, compared to 12 HCs (Ehlen et al., 2014). When compared to HCs, patients in both DBS groups uttered fewer words with DBS OFF; however, there were no substantial differences between the DBS cohorts post-DBS. When comparing DBS ON vs. OFF, *post-hoc* analysis revealed that there was a notable reduction in the number of words produced with VIM DBS, particularly in phonemic fluency. Conversely, STN DBS improved phonemic fluency, but this did not suffice to significantly change the overall performance. Decreasing phonemic fluency in patients with VIM DBS was found to be correlated with increasing stimulation amplitudes (Ehlen et al., 2014). Another study by the same group focusing on verbal fluency tasks showed that patients with bilateral VIM DBS produced fewer words than controls, which also worsened with DBS ON state, and was correlated with more anterior electrode positions (Ehlen et al., 2017). VIM DBS can also affect spontaneous language production in ET patients. Ehlen et al. (2016) found that the number of words produced in the verbal fluency tasks was significantly lower in the VIM DBS ON vs. OFF status. A retrospective analysis compared spontaneous language production in a total of 39 participants with VIM DBS for ET, STN DBS for PD, and HCs (Tiedt et al., 2021). Although the study did not show differences in lexical (phonemic) frequency among the three groups, post-hoc analysis showed significantly lower word frequency in the VIM DBS group (with bilateral DBS in 13 out of 14 patients) compared to the STN DBS group while OFF DBS; however, with DBS ON, word frequency improved in the same group. Additionally, both DBS groups showed a lower proportion of open-class words relative to closed-class words when compared to the HC group (Tiedt et al., 2021). To study the effect of VIM DBS on language processing rather than production, Krugel et al. (2014) used an acoustic lexical decision task in a comparative case–control study and found that VIM DBS slowed down word decisions in 10 ET patients and reduced N400 potentials when compared to STN DBS in 14 PD patients and 12 matched HCs.

Three long-term studies followed ET patients for 2 or more years (Heber et al., 2013; Klein et al., 2017; Wang et al., 2020). Among them, the longest study followed 9 ET patients prospectively over 6 years (Heber et al., 2013), who underwent thalamic VL nucleus DBS and were evaluated for cognitive changes before surgery, as well as 1 and 6 years thereafter with DBS ON and OFF. No differences were found in tasks of verbal fluency, memory, executive and intellectual functions comparing pre-surgery, DBS ON, and OFF at 1- and 6-years post-surgery. No medications were changed after surgery. A retrospective review of prospectively collected data, following 9 ET patients with bilateral VIM DBS for up to 2 years (Wang et al., 2020), showed no significant changes in memory, but improvement in anxiety and depression that were seen as early as 1-month post-DBS (DBS OFF) and persisted at 1- and 2-year follow-up evaluation (DBS ON). However, all ET medications were stopped post-DBS, which could possibly affect anxiety and depression. Klein et al. (2017) followed 26 ET patients with bilateral VIM DBS for more than 2 years and analyzed cognitive outcomes pre- and post-DBS relative to their age at surgery. The study found no differences in outcomes between the two groups; however, patients older than 70 years of age had a worse score on the Mattis Dementia Rating Scale preoperatively, which improved post-DBS. Medication changes post-DBS were not reported in this study.

The largest study on cognitive outcomes in ET was a retrospective analysis of 50 ET patients with unilateral ($n = 37$) and bilateral ($n = 13$) VIM DBS (Jones et al., 2020). The study assessed 6 cognitive domains pre- and post-DBS (> = 1 year), while ET medications were continued, and analyzed changes according to baseline characteristics, total electric energy delivery (TEED), and surgery-related complications. Group analysis revealed no significant longitudinal pre- to post-DBS changes for all cognitive domains. *Post-hoc* analysis by age at tremor onset revealed working memory improvement for younger onset ET (<38 years) after DBS surgery, and complications vs. no complications showed a significant decrease in verbal memory in patients with complications after surgery. Additionally, *post-hoc* analysis of cognitive changes by DBS laterality (unilateral vs. bilateral DBS; left vs. right side) did not show any differences in outcomes.

To address the practice effects of repeated exposures to neuropsychological tests, a recent retrospective study utilized regression-based reliable change indices to better objectively assess the impact of DBS on cognition (Kielb et al., 2022). Thirty ET patients with unilateral VIM-DBS underwent neuropsychological evaluation around 6–7 months pre-DBS and 6–7 months post-DBS. Group-level analysis showed no significant changes in cognitive test scores pre- and post-DBS, and individual reliable change (RC) scores showed that 60% of the sample had a stable performance on all tests, and 36.7% had one significant decline in RC score, which represents normal variability. There was no report on whether medications were changed post-DBS in this study.

Looking into cognition-related mood variables, a prospective comparative study of mood, specifically anger, in patients with DBS for PD (STN or GPi) or ET (VIM) showed that STN and GPi DBS were associated with significantly higher anger across pre- to post-DBS as compared to VIM DBS (Burdick et al., 2011). There was no significant change in the levodopa equivalent dose post-DBS placement in PD patients, but whether there were changes in ET medications post-DBS was not reported in this study.

cZi/PSA DBS

Two studies reported on cognitive outcomes in ET patients post unilateral and bilateral cZi-DBS (Fytagoridis et al., 2013; Philipson et al., 2019). Both studies recruited patients prospectively and followed patients for a year after DBS surgery. Fytagoridis et al. specifically assessed verbal fluency in 17 ET patients with bilateral and unilateral DBS and found that there was a significant decrease in verbal fluency 3 days post-DBS surgery while stimulation was still OFF. This change was not detectable at the group level 1-year post-DBS at both OFF and ON states, hence it is possible that the early decreased fluence could be due to lesioning effect or acute changes postoperatively. It is notable that 4 patients with a 50% reduction in verbal fluency 3 days post-DBS had a sustained reduction of 38% after 1 year. Philipson et al. assessed multiple cognitive domains (memory, executive function, attention, and verbal) in 26 ET patients and found no significant changes 12 months post-DBS at the ON state compared to baseline pre-DBS

except for a statistically significant but mild decline in semantic verbal fluency. There were no differences in cognitive measures in patients with bilateral vs. unilateral DBS. Medication changes post-DBS were not reported in this study.

Discussion

DBS remains a highly effective treatment for pharmacologically refractory ET, and its cognitive safety is of utmost importance to patients. Clinically meaningful cognitive outcomes can be hard to define and study, and long-term follow-up of a large patient cohort with cognitive measures can be challenging. The most recent review on cognitive outcomes in patients with ET who underwent DBS included eight studies (Cernera et al., 2019). By expanding our search to PubMed and Web of Science, and systematically searching the up-to-date literature, we were able to identify a total of 20 studies that met the inclusion criteria up to March 2023. In this systematic review, we detailed these 20 studies that dissected a wide range of cognitive outcomes in ET patients who underwent VIM, VL/VLp, or cZi/PSA DBS, followed over a short and long term.

We found a high degree of heterogeneity in study design, sample size, neuropsychological battery, medication status, and statistical analysis. Only one study was a prospective randomized clinical trial among the 13 prospective studies, and seven were retrospective. Most studies were small, with a median number of 22 ET patients in each study (ranging from 2 to 71). Most studies had short-term follow-up post-DBS, with a median follow of 12 months (ranging from 3 to 70 months). In studies comparing pre- and post-DBS cognitive outcomes, tremor medications were either unchanged although tremor was shown to be improved (Tröster et al., 1999; Fields et al., 2003; Heber et al., 2013; Jones et al., 2020; Wang et al., 2021), changed without a significant effect on cognitive outcomes (Wang et al., 2020; Dhima et al., 2021), changed and controlled for (Woods et al., 2003), or not reported (Burdick et al., 2011; Fytagoridis et al., 2013; Klein et al., 2017; Philipson et al., 2019; Kielb et al., 2022). Statistical analyses and investigating individual-level change over time were highly variable among the reviewed literature. Inconsistent evaluation of change in cognitive function across studies deemed difficult to compare results from one study to another sufficiently. The most robustly studied cognitive outcome was language, specifically verbal fluency speed and other aspects of language functioning. Both VIM and cZi/PSA DBS have been documented to adversely influence verbal fluency and language production. Studies showed that VIM DBS resulted in a decrease in speeded phonemic fluency (Ehlen et al., 2014, 2016, 2017), slowing down in word decision-making (Krugel et al., 2014), and reduced use of open class words (Tiedt et al., 2021). Ehlen and colleagues also documented worse verbal fluency particularly during DBS ON compared to OFF (Ehlen et al., 2016, 2017), with increasing stimulation amplitude (Ehlen et al., 2014) and anterior electrode positions in the VIM (Ehlen et al., 2017).

In cZi/PSA DBS, Fytagoridis et al. (2013) hinted at a possible lesioning effect of DBS on verbal fluency as it decreased 3 days post DBS surgery in the OFF state, which became undetectable on the group level 1 year post-DBS in the ON state, although it continued to be mildly detectable in a small number of patients. Additionally, Philipson et al. (2019) also showed a mild decrease in verbal fluency 12 months post-DBS; however, the only comparison made was to the pre-DBS baseline rather than to post-DBS in the OFF state. Hence, it remains unclear if the decline in verbal fluency is due to a long-lasting lesioning effect vs. stimulation effect. None of the studies evaluated the potential correlation of the number of microelectrode passes with cognitive changes in patients with ET, except one on a correlation of cognitive outcome (anger) with the number of passes of the microelectrode in STN and GPi DBS in patients with PD compared to VIM DBS in patients with ET (Burdick et al., 2011).

With the advent of cZi/PSA DBS for ET patients, comparative studies are necessary to compare cZi/PSA DBS vs. VIM DBS on their effect on cognitive outcomes, especially looking into the effect of DBS parameters on such outcomes, given that cZi/PSA DBS is proposed to target a smaller anatomical area effectively and possibly more efficiently treating tremor (Herzog et al., 2007; Barbe et al., 2011, 2018; Sandvik et al., 2012; Xie et al., 2012; Ramirez-Zamora et al., 2016; Blomstedt et al., 2018; Al-Fatly et al., 2019; Dembek et al., 2020).

Multiple studies looked at the effect of laterality on cognitive outcomes. Most analyses were *post-hoc*. Put together, left-sided VIM stimulation could affect different cognitive domains including verbal abstraction, word recall, and verbal memory performance (Loher et al., 2003; Woods et al., 2003; Dhima et al., 2021). A longer or larger left-sided pulse width (>120 μs) was correlated with overall cognitive decline in one study (Woods et al., 2003) and verbal memory decline in another (Dhima et al., 2021). It was postulated that longer or larger pulse width may activate larger-diameter myelinated axons which could disrupt frontal projections within the cerebello-thalamo-cortical network, potentially affecting verbal memory (Lenka et al., 2017; Dhima et al., 2021), although it is also possible that the increased TEED as a result of larger pulse width could also stimulate the adjacent unwanted fiber causing cognitive side effects. Additionally, left-sided VIM DBS for tremors caused by ET, PD, or MS was associated with worse word recall across all three diseases in a small study (Loher et al., 2003). On the other hand, two studies did not find any significant differences in cognitive outcomes pre- and post-DBS when analyzed by DBS laterality (unilateral vs. bilateral DBS; left vs. right side) (Philipson et al., 2019; Jones et al., 2020).

Based on this review of literature, substantial cognitive decline after VIM or cZi/PSA DBS in ET patients appears to be rare, suggesting that both procedures are generally safe from a cognitive standpoint, especially after taking into consideration their overall benefits on patients' quality of life (Tröster et al., 1999; Fields et al., 2003; Nazzaro et al., 2012). While overall safe, there are conflicting results regarding the impact on verbal fluency and other aspects of language function. Most studies also have a small sample size, limiting the statistical power of the results obtained, with only one study of a randomized trial. In addition, cognitive changes induced by medication are largely neglected in the literature. There is no standard requirement on the medication changes after VIM DBS for ET, although the commonly used medications for ET, such as propranolol, primidone, and topiramate, could have sedative side effects on patients, which could possibly have beneficial effects on cognitive function if they are reduced or stopped after the DBS surgery. As such, future studies that parametrically manipulate the

location and laterality of the active contact and stimulation parameters might be necessary to test specific hypothesis pertaining to the effect of stimulation on specific cognitive outcomes. Additionally, long-term prospective blinded randomized controlled trials should be designed, considering the medication changes post-DBS and DBS ON/OFF status as a potential confounder for cognitive outcomes. Statistical analysis that considers practice effects and effect size is also warranted to objectively ascertain true impact. Standardization of test battery will also allow a better understanding of the impact on specific cognitive domains.

Author contributions

JA: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. ML: Formal analysis, Investigation, Writing – review & editing. MP: Investigation, Writing – review & editing. WA: Investigation, Writing – review & editing. HH: Investigation, Writing – review & editing. PW: Investigation, Writing – review & editing. TX: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2024.1319520/full#supplementary-material

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Tractography-based DBS lead repositioning improves outcome in refractory OCD and depression

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Deep brain stimulation (DBS) of the anterior limb of the internal capsule (ALIC) has been used to treat refractory obsessive-compulsive disorder (OCD) and depression, but outcomes are variable, with some patients not responding to this form of invasive neuromodulation. A lack of benefit in some patients may be due to suboptimal positioning of DBS leads. Recently, studies have suggested that specific white matter tracts within the ALIC are associated with improved outcomes. Here, we present the case of a patient who initially had a modest improvement in OCD and depressive symptoms after receiving DBS within the ALIC. Subsequently, he underwent unilateral DBS lead repositioning informed by tractography targeting the ventrolateral and medial prefrontal cortex's connection with the mediodorsal thalamus. In this patient, we also conducted post-implant and post-repositioning diffusion imaging and found that we could successfully perform tractography even with DBS leads in place. Following lead repositioning into tracts predictive of benefit, the patient reached responder criteria for his OCD, and his depression was remitted. This case illustrates that tractography can potentially be used in the evaluation and planning of lead repositioning to achieve therapeutic outcomes.

KEYWORDS

deep brain stimulation, OCD, anterior limb of the internal capsule, diffusion imaging, tractography, fMRI

Introduction

Deep brain stimulation (DBS) of the anterior limb of the internal capsule (ALIC) has been used to treat refractory obsessive-compulsive disorder (OCD) (Mallet et al., 2008; Denys et al., 2010; Luyten et al., 2016; Mosley et al., 2021) and depression (Malone et al., 2009; Dougherty et al., 2015; Bergfeld et al., 2016). However, approximately 30–40% of patients do not respond to DBS for OCD (Denys et al., 2020). Moreover, many of the initial studies using ALIC DBS to treat refractory depression have inconsistent outcomes (Malone et al., 2009; Dougherty et al., 2015; Bergfeld et al., 2016). It is possible that suboptimal positioning of DBS leads contributes to a lack of benefit in some patients. Recently, studies have suggested that positive DBS outcomes in OCD and depression are associated with

modulation of white matter tracts coursing between the ventrolateral and medial prefrontal cortex (PFC), through the ALIC, and subcortically to the medial thalamus and subthalamic nuclei (STN) (Baldermann et al., 2019; Li et al., 2021).

Here, we report the case of a patient with DBS of the ALIC for OCD who underwent unilateral DBS lead repositioning after having an initial limited therapeutic response. Structural and diffusion-weighed imaging (DWI) were performed pre-operatively, post-implant, and following lead repositioning. We describe the patient's history and structural neuroimaging to support the role of using tractography to optimize DBS surgical planning.

Case description

The patient is a 53-year-old man with a history of severe, treatment-refractory OCD and co-morbid severe major depressive disorder (MDD). His harm-based OCD began in his teenage years, and he was formally diagnosed at age 28. His OCD primarily surrounds shame- and harm-based obsessions associated with extensive checking behaviors. At the time of evaluation, the patient described his OCD symptoms as near constant, feeling "intensely hopeless and anxious" to the point where he found it difficult to eat. He had not been going to work for 1–2 days each week due to the severity of his symptoms. In turn, the high level of distress from his OCD symptoms had caused him to feel depressed and isolated. He found it difficult to take pleasure in his daily activities, and his motivation to get out of bed and go to work was low.

Numerous medications, including multiple selective serotonin reuptake inhibitors, multiple serotonin and norepinephrine reuptake inhibitors, augmentation with multiple antipsychotics, clomipramine, and intravenous ketamine, were trialed to treat his OCD and MDD with limited benefit or intolerable side effects. He did not respond to repetitive transcranial magnetic stimulation for OCD or depression. He underwent extensive psychotherapy, including exposure-response prevention, with limited benefit. He also attended partial hospitalization programs and intensive outpatient programs, specializing in OCD with a limited response. Given his history of severe, treatment-refractory OCD and MDD, the patient was deemed an appropriate candidate for DBS targeting the ALIC for both disorders (Mallet et al., 2008; Malone et al., 2009; Denys et al., 2010; Dougherty et al., 2015; Bergfeld et al., 2016; Luyten et al., 2016; Denys et al., 2020; Mosley et al., 2021). Before DBS surgery, both his OCD and depression symptoms were in the severe to extreme range, with a Yale-Brown Obsessive Compulsive Scale (YBOCS) of 36 and a Patient Health Questionnaire-9 (PHQ-9) of 25.

Pre-operative T1-weighted structural magnetic resonance imaging (MRI) and DWI (55-direction HARDI, $b = 2000$) were acquired on a 3 T GE scanner with a eight-channel head coil for the purposes of surgical planning. Two quadripolar DBS leads (3,387; Medtronic, Minneapolis, MN) were stereotactically implanted within the bilateral ventral ALIC, with the middle contacts being targeted close to the bed nucleus of the stria terminalis (BNST). The right lead was positioned approximately 5 mm closer to the midline compared with the left lead position on the MRI (Figures 1A,B). The middle contacts of the right lead were positioned within the BNST. Standard stimulation programming was initiated 4 weeks after implantation. The patient experienced acute improvements in mood and anxiety with stimulation from the left lead in the C + 2- monopolar configuration at 7 mA. However, DBS using the right lead was discontinued after several months due to a lack of benefit even at high currents across multiple contacts. The patient achieved a partial benefit in OCD symptoms with a reduction in YBOCS to 25 (28% improvement compared to immediately before DBS) and improvement in depression (PHQ-9 reduced to 14; 40% improvement) after 1 year of treatment (Figure 1C). During this time, medications were not altered, and the patient was engaged in weekly ERP.

There was a concern that the lack of benefit from the right lead was due to its medial location relative to the therapeutic left lead. Whole-brain tractography was performed from an estimated volume of activated tissue (VAT) from the left therapeutic C + 2- configuration using the Lead-DBS software package (Cieslak et al., 2021). The tractography was performed using the pre-implant DWI and post-operative T1-weighted structural MRI for lead localization. The left VAT demonstrated structural connectivity to the medial PFC, mediodorsal thalamus, and STN through tracts previously associated with benefit for OCD (Figure 2, left panel). However, the right VAT was medial to these tracts predictive of response. Instead, the right VAT was structurally connected with the stria terminalis and ansa peduncularis, tracts that project to the temporal lobe and amygdala (Figure 2, middle panel).

At approximately 2 years post-implantation, a right lead repositioning was attempted due to the patient's significant residual OCD and mood symptoms. During the repositioning, the new lead was targeted along a trajectory that was informed by tractrography using the pre-implant DWI. Tractography was used to identify the anterior thalamic radiation (ATR) connecting the medial and ventrolateral prefrontal cortex with the mediodorsal thalamus. The right DBS lead was repositioned so the dorsal contacts were within the ATR based upon the tractography, mirroring the more lateral placement of the left therapeutic lead (Figures 1A,B).

Following repositioning and subsequent reprogramming, stimulation from the right C + 1- contact at 5 mA led to an acute improvement in mood and anxiety. The patient's OCD improved by 39% (a reduction in YBOCS to 22) from before DBS. His depressive symptoms also improved by 64% (reduction in PHQ-9 to 9) relative to before DBS (Figure 1C). Additional improvement in OCD symptoms was observed at the last follow-up, 22 months after lead repositioning, with the last YBOCS being 20 (a reduction of 44% compared to prior to DBS implantation). While the patient did still have a moderate amount of residual symptoms, he noted that the benefit for his OCD from DBS was significant and meaningful to him, allowing him to work and engage in relationships, which was previously difficult given the nature of his obsessions. Importantly, his improvement in mood was also substantial; he noted that he was better able to cope in the face of stressors and had a sustained improvement in his motivation and energy with DBS.

Using the pre-implant DWI, we conducted tractography from the stimulation field corresponding with the repositioned right lead (Figure 2, right panel). After lead repositioning, there was an increase in the fraction of total streamlines from the right VAT to the right thalamus, brainstem, and right frontal pole. These tractography results

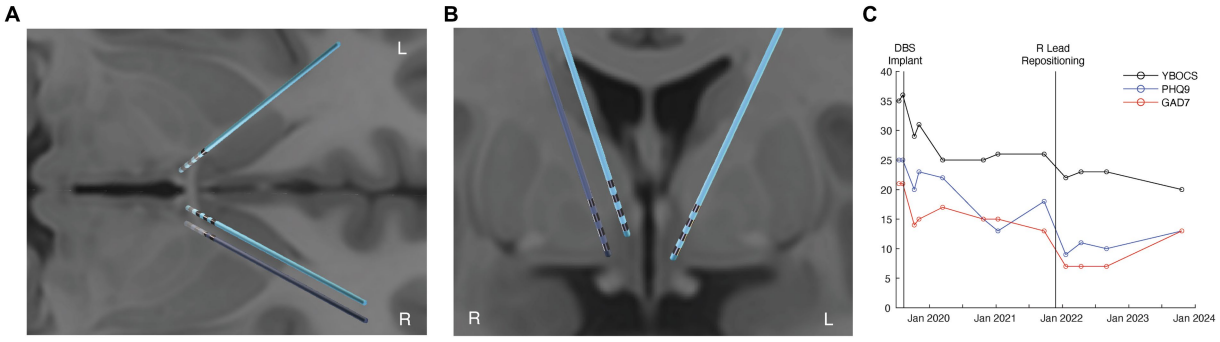

FIGURE 1
Improved OCD and depression outcomes from tractography-informed DBS repositioning. **(A)** axial view of the original (light blue) and repositioned DBS leads (dark blue). **(B)** coronal view of the original (light blue) and repositioned DBS leads (dark blue). **(C)** clinical improvement in OCD (YBOCS), depression (PHQ-9), and anxiety (GAD7) scores before DBS, after DBS, and following right lead repositioning.

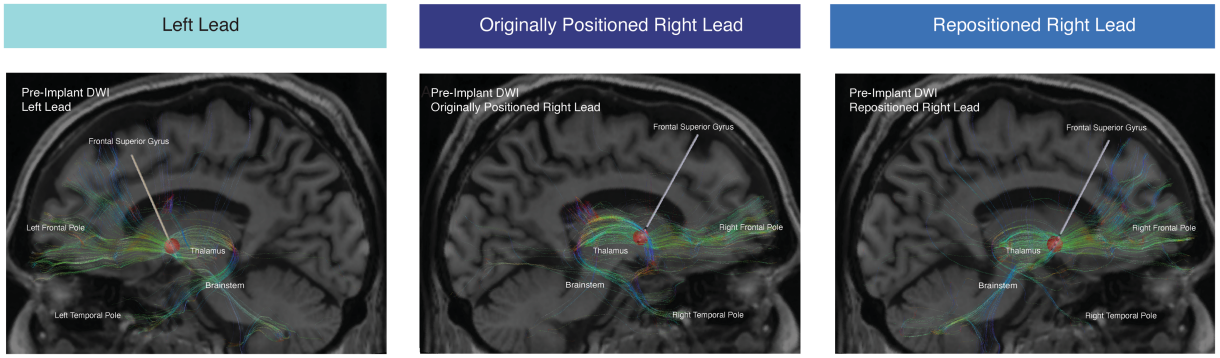

FIGURE 2
Tractography from estimated VAT. Tractography from the estimated VAT from the therapeutic active left contact (5 mA C + 2-) (left panel), right contact (5 mA C + 1-) from the originally positioned right lead (middle panel), and right contact from the repositioned right lead (right panel). Tractography was conducted with the pre-implant DWI.

are consistent with prior studies demonstrating that increased structural connectivity to these regions is correlated with improved DBS outcomes for OCD (Figures 2, 3) (Baldermann et al., 2019; Li et al., 2021). There was also decreased connectivity between the VAT and the right temporal lobe following repositioning, which has been associated with worse outcomes (Figures 2, 3).

In this case, we were able to use personalized tractography to evaluate the need for DBS lead repositioning because DWI had been acquired prior to the DBS implant. However, in many cases, pre-implant DWI may not have been acquired. For this reason, we were interested in seeing if it was possible to perform reliable tractography using DWI that is acquired after DBS implantation with leads in place. With local IRB approval and written patient consent, we reacquired T1-weighted structural MRI and DWI (29-direction, b = 1,000) following the original DBS lead implantation as well as after the repositioning. We were able to successfully reconstruct tracts passing through the estimated VAT from the originally positioned right lead, the repositioned right lead, and the left lead, using both the post-implant and post-repositioning DWI with the DBS leads in place (Supp Fig S1). We validated the tractography using the post-implant DWI against the pre-implant results, demonstrating a strong correlation between the streamline counts from the VAT to other parcellated brain regions (Horn et al., 2019) (Figure 4, $r_{R\ Lead\text{-}Original} = 0.89$; $p = 2.4 \times 10^{-39}$, $r_{R\ Lead\text{-}Repositioned} = 0.84$; $p = 6.7 \times 10^{-31}$, $r_{L\ Lead} = 0.86$; $p = 2.6 \times 10^{-34}$). We also validated the tractography from the post-repositioning DWI against the pre-implant and post-implant tractography (Supplementary Figure S2). To the best of our knowledge, this is the first demonstration that tract reconstructions can be performed using post-implant DWI in a patient receiving DBS for OCD.

Methods

MRI

MRI scans were acquired on a 3 Tesla scanner (Discovery MR750, GE Healthcare, Chicago, IL). We collected T1- and T2-weighted structural scans and pre-implantation DWI (55-direction HARDI, $b = 2000$), T1-weighted structural and post-implantation DWI (29-direction, $b = 1{,}000$), and T1-weighted structural and DWI post-repositioning (29-direction, $b = 1{,}000$).

Data analysis

DWI scans were preprocessed using QSIprep (Tournier et al., 2019). MP-PCA denoising as implemented in MRtrix3's dwidenoise was applied with a five-voxel window, and then Gibbs unringing was performed using MRtrix3's mrdegibbs (Andersson and Sotiropoulos, 2016). B1 field inhomogeneity was corrected using dwibiascorrect from MRtrix3 with the N4 algorithm. FSL's eddy was used for head motion correction and eddy current correction (Friston et al., 2011). Shells were aligned post-eddy. Eddy's outlier replacement was run. The DWI time series were resampled to ACPC, generating a preprocessed DWI run in ACPC space with 1 mm isotropic voxels. Using Lead-DBS (Cieslak et al., 2021), a MATLAB toolbox for DBS electrode reconstruction and simulation of DBS stimulation, T1, T2, and DWI scans were co-registered using SPM (Avants et al., 2008) and normalized using ANTs (Schoenecker et al., 2009; Yeh et al., 2010; Fonov et al., 2011), after which DBS electrodes were reconstructed and manually localized. White matter tracts were reconstructed from diffusion imaging data using generalized q-sampling (Baniasadi et al., 2020). The volume of activated tissue (VAT) was modeled for monopolar stimulation using FastField (Rushmore et al., 2022), and the VATs were used as seeds to generate connectivity to parcels from the Harvard-Oxford cortical and subcortical atlas (Horn et al., 2019).

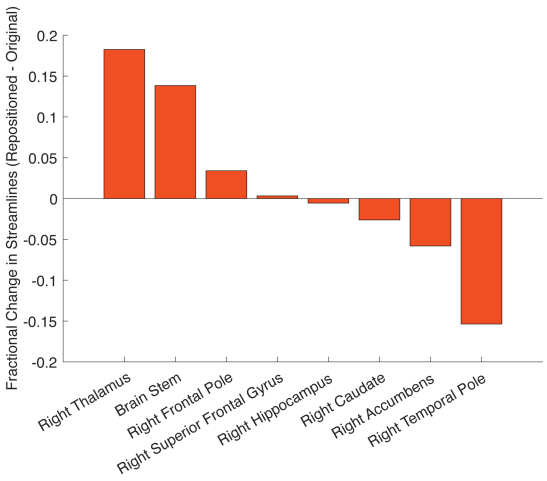

FIGURE 3
Change in structural connectivity following DBS repositioning. Change in streamline counts between the repositioned and originally positioned active contact on the right leads to different brain regions. Streamlines are derived from tractography using the pre-implant DWI.

Discussion

While DBS is used to treat refractory OCD, approximately 30–40% of patients do not respond, and many still have significant residual symptoms after treatment has been optimized. Typically, the region targeted in DBS for OCD is the ventral ALIC, which encompasses a large area with associated structures including the nucleus accumbens, BNST, and overlying white matter tracts. Recently, studies have suggested that engagement of particular white matter tracts connecting ventrolateral and medial PFC through central ALIC to the thalamus and STN is an important predictor of benefit for outcomes for OCD and depression (Baldermann et al., 2019; Li et al., 2021; Gadot et al., 2023; Lai et al., 2023). Moreover, there is increasing interest in using

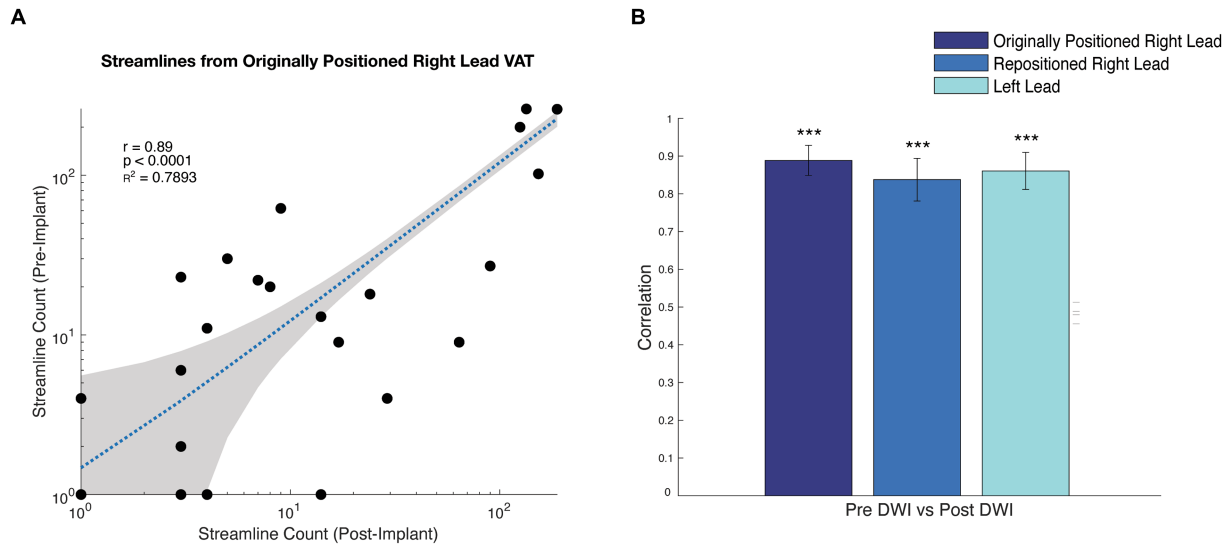

FIGURE 4
Correlation between tractography results from pre-implant, post-implant, and post-repositioning DWI. **(A)** Scatterplot of the streamline counts to each parcel for the original lead positioning using pre- and post-implant DWI. **(B)** bar graph showing the correlation coefficient of the streamline counts between parcellated regions and the VAT corresponding with the originally positioned right lead, repositioned right lead, and left lead comparing the pre-implant and post-implant DWI. *** $p < 0.0001$ based upon a t-test.

personalized connectomes based on tractography to inform DBS targeting to account for individual differences in anatomy. Together, these findings suggest that one source of variability in DBS outcomes may be the positioning of leads relative to tracts predictive of improved outcomes.

Here, we report the case of a patient who achieved additional improvement after DBS lead repositioning targeted at white matter tracts predictive of DBS responsiveness. Before repositioning, many of the contacts were near the stria terminalis and ansa peduncularis projecting to the amygdala complex, and the patient had limited benefits for OCD and depression. Tractography was then performed using pre-implant DWI to identify white matter tracts connecting the medial PFC to the mediodorsal thalamus and STN, and DBS leads were repositioned to a region containing these tracts within the ALIC. Subsequently, the patient experienced additional improvement in his OCD and depressive symptoms, consistent with prior studies.

Furthermore, we demonstrated that it is possible to reproduce tract reconstructions with DBS leads in place. Given that MRI artifacts from leads can interfere with tract reconstruction, we validated that the structural connectivity estimates from stimulation VATs that we obtain with post-implant DWI are comparable to those estimated from a pre-implant scan. However, structural connectivity results derived from post-repositioning DWI had weaker correlations to pre-implant and post-implant DWI, specifically at the right repositioned lead, perhaps implying some change in white matter integrity following DBS repositioning surgery. The ability to reconstruct tracts using DWI with DBS leads in place is important given that pre-operative DWI is not always available in many cases.

Over a third of patients do not respond to DBS for OCD, highlighting the importance of determining how suboptimal lead placement or other factors contribute to poor outcomes. Here, we demonstrate that tractography can be used to evaluate whether leads are optimally positioned near white matter tracts predictive of benefit. Furthermore, we describe a case in which DBS lead repositioning informed by tractography improved clinical outcomes for a patient who was a partial responder. This case demonstrates the importance of anatomical targeting in clinical response. Future studies tracking lead repositioning outcomes in a larger cohort of OCD and DBS patients will be needed to validate these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the University of California, San Francisco. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GB-P: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. NS: Methodology, Writing – review & editing. AF: Investigation, Writing – review & editing. TN: Investigation, Writing – review & editing. MM: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing. LS: Conceptualization, Funding acquisition, Investigation, Methodology, Writing – review & editing. PL: Investigation, Writing – review & editing. PS: Investigation, Methodology, Writing – review & editing. AL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2023.1339340/full#supplementary-material

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DiMANI: diffusion MRI for anatomical nuclei imaging—Application for the direct visualization of thalamic subnuclei

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The thalamus is a centrally located and heterogeneous brain structure that plays a critical role in various sensory, motor, and cognitive processes. However, visualizing the individual subnuclei of the thalamus using conventional MRI techniques is challenging. This difficulty has posed obstacles in targeting specific subnuclei for clinical interventions such as deep brain stimulation (DBS). In this paper, we present DiMANI, a novel method for directly visualizing the thalamic subnuclei using diffusion MRI (dMRI). The DiMANI contrast is computed by averaging, voxelwise, diffusion-weighted volumes enabling the direct distinction of thalamic subnuclei in individuals. We evaluated the reproducibility of DiMANI through multiple approaches. First, we utilized a unique dataset comprising 8 scans of a single participant collected over a 3-year period. Secondly, we quantitatively assessed manual segmentations of thalamic subnuclei for both intra-rater and inter-rater reliability. Thirdly, we qualitatively correlated DiMANI imaging data from several patients with Essential Tremor with the localization of implanted DBS electrodes and clinical observations. Lastly, we demonstrated that DiMANI can provide similar features at 3T and 7T MRI, using varying numbers of diffusion directions. Our results establish that DiMANI is a reproducible and clinically relevant method to directly visualize thalamic subnuclei. This has significant implications for the development of new DBS targets and the optimization of DBS therapy.

KEYWORDS

thalamus, thalamic subnuclei, thalamus parcellation, diffusion MRI, direct visualization, DiMANI, DBS

1 Introduction

The thalamus is a centrally located brain structure involved in a myriad of sensory, motor, and cognitive processes with direct and indirect connections throughout the cortical brain. As such, it has been the focus of many neuroimaging studies with applications in movement, psychiatric, and other mental disorders [see Boelens Keun et al. (2021) for a review].

What gives the thalamus such diverse capabilities and roles is its heterogeneous constitution comprising many smaller subnuclei, each with its own set of structural connections. While historically thalamus subdivision and nomenclature have differed across many key histological and postmortem reports (Mai and Majtanik, 2018), seven morphological groups have been identified. The anterior nuclear group is associated with visual memory and emotional, cognitive, and executive functions. The lateral group is involved in spatial navigation, limbic functions, and visual information processing. The ventral group partakes in motor functions, language, and somatosensory information processing. The intralaminar group is involved in attention regulation, salience, and arousal. The medial group is associated with vigilance, awareness, executive functioning, emotion processing, and memory. The reticular nucleus is involved in the generation of sleep spindles and other processes as theorized in the "searchlight hypothesis" (Crick, 1984). Finally, the posterior nuclear group processes and integrates sensory information from visual, auditory, and multisensory modalities (Boelens Keun et al., 2021).

Clinical treatments and therapies, such as deep brain stimulation (DBS) and focused ultrasound, take advantage of the different functions subserved by these different groups by targeting specific subsubnuclei which have functions related to a given disorder (see Supplementary Table 1). For example, the ventral intermediate nucleus of the thalamus (Vim), part of the ventral group, is a target for DBS and thalamotomy for tremor-related movement disorders such as essential tremor (ET) (Dallapiazza et al., 2019). The anterior thalamus has been extensively targeted for the treatment of refractory epilepsy (Bouwens van der Vlis et al., 2019), although it is not always clear whether it is the anteroventral (AV), the anterodorsal (AD) or even part of the ventralanterior (VA) nucleus that is being stimulated. The mediodorsal nucleus (MD), part of the medial group, has been tested as a target for obsessive-compulsive disorder (Maarouf et al., 2016). The centromedian (CM), part of the intralaminar group, is one DBS target for the treatment of Tourette's syndrome (Casagrande et al., 2019) and generalized epilepsy, a.k.a. Lennox-Gastaut syndrome (Aungaroon, 2022). Of note, the intralaminar subnuclei of the thalamus have also been targeted using DBS (Schiff et al., 2007) and low-intensity focused ultrasound (Monti et al., 2016) to restore routine behavior and consciousness in patients in a minimally conscious state following brain injury. Using DBS in the ventral posterior nucleus, part of the ventral group, has shown promise in the treatment of neuropathic pain (Boccard et al., 2013). Many of these targets are also under consideration as targets for lesioning procedures such as thalamotomy and focused ultrasound. While many of these thalamic DBS approaches have demonstrated significant benefits to patients, others were unsuccessful. Further, even the standard DBS and lesioning approaches often suffer from variable patient outcomes. One reason for heterogenous results in clinical efficacy might stem from the difficulty to directly visualize and target specific subnuclei of the thalamus on clinical brain images as well as interindividual variability in the size, shape and geometric configuration of thalamic subnuclei.

The most commonly used magnetic resonance imaging (MRI) contrasts in the clinical setting (i.e. T1 and T2) do not show individual thalamic subnuclei due to poor contrast within the thalamus. Therefore, direct targeting for DBS using current clinical imaging protocols is extremely difficult. This has led surgical teams to use templates and atlases, which do not account for inter-individual anatomic variability, and are oftentimes derived from individuals outside of the patient's population demographics (e.g., age, disease state). Several groups have worked to develop new imaging methods for direct visualization, including susceptibility weighted imaging (SWI) (Abosch et al., 2010; Najdenovska et al., 2019), quantitative magnetic susceptibility mapping (QSM) (Deistung et al., 2013; Chiang et al., 2018), or white-matter nulled T1 imaging, such as FGATIR (Sudhyadhom et al., 2009; Hoch and Shepherd, 2022), 3D-EDGE (Middlebrooks et al., 2021), and WMn-MPRAGE (Su et al., 2019). However, these methods have drawbacks. Despite using a 7 Tesla (7T) MRI scanner, Najdenovska et al. (2019) demonstrated that direct visualization of the Vim in SWI images was not always possible, and QSM typically involves long acquisition times as well as complex imaging protocols and reconstruction algorithms making them difficult to use routinely in the clinic. The standard FGATIR acquisition—without expert parameter adjustments—can suffer from poor contrast at 7T due to B1 inhomogeneity (Tao et al., 2022). Additionally, 3D MRI acquisitions schemes, such as SWI and MPRAGE-based sequences, are extremely sensitive to motion, a substantial issue when working with movement disorder patients. Finally, several of these methods are not common practice in the clinical world as they require MR expertise and computational capabilities not available in most non-academic centers.

Diffusion MRI (dMRI) has been extensively used to attempt to uncover the sub-territories of the thalamus. The two main strategies involve tractography and clustering based on local fiber orientation. The former computes the connectivity of each voxel in the thalamus to multiple cortical regions of interest (ROIs) and assigns each voxel a label based on the relative connectivity strength to these ROIs (Behrens et al., 2003). The latter models local fiber orientation distributions or the dominant diffusion orientation at each voxel within the thalamus and then generates parcels via a clustering approach (Mang et al., 2012; Battistella et al., 2017; Iglehart et al., 2020). Tractography-based parcellation results, the most used dMRI method to date (Su et al., 2019; Iglehart et al., 2020), are heavily dependent on the targets being included in the tractography analysis. Inclusion or exclusion of one cortical region will change the results (e.g., final number of clusters, cluster assignment, border location). Additionally, these methods typically use a winner-take-all approach in which a voxel is assigned to a territory based on its relatively high connectivity to a target (e.g. motor cortex) (Behrens et al., 2003) regardless of the fact that it may also be highly connected to another region. In fact, many thalamic subnuclei are connected to multiple brain regions [Table 1 from Boelens Keun et al. (2021)].

Here we present a novel method to directly visualize the subnuclei of the thalamus that can be implemented on previously acquired dMRI datasets. The proposed method, termed DiMANI, is based on the voxelwise average of diffusion weighted volumes to enhance the anatomical contrast within the tissue, allowing for the direct distinction of thalamic subnuclei in individuals.

The reproducibility of the proposed method was evaluated in several ways. First, on the acquisition side, a unique dataset

consisting of 8 scans of a single participant collected over a 3-year period were segmented and compared (test-retest). Second, on the image post-processing side, manual segmentations of thalamic subnuclei were quantitatively evaluated for both intra-rater as well as inter-rater reliability. Third, on the clinical side, DiMANI was evaluated in data from several DBS patients and qualitatively correlated with electrode localization and clinical observations. Finally, we show that DiMANI provides similar contrast at 3T and 7T with varying number of diffusion directions.

2 Methods

2.1 Subjects

Six ET patients were enrolled from the University of Minnesota DBS program. Inclusion criteria required patients to have a diagnosis of Essential Tremor and be suitable candidates for Vim-DBS surgery. The study did not interfere or change the patients' routine treatment protocol except for adding one extra 7T MRI scan prior to surgery. The patient cohort consisted of four males and two females with an average age of 61.2 ± 12.3 years and an average disease duration of 22.5 ± 10.9 years. One recruit from the University of Minnesota volunteer pool served as a healthy control and was scanned eight times (male, 53 years at the time of the first scan and 56 years at the eighth). Finally, one healthy control, subject 100610 (male, 26–30 years), and one patient, subject 85236 (male, 69 years), were downloaded from the Human Connectome Project (HCP) and from the Parkinson's Progression Markers Initiative (PPMI) databases, respectively (https://www.humanconnectome.org, https://www.ppmi-info.org). The study was approved by the Institutional Review Board at the University of Minnesota and informed consent was obtained from all participants prior to inclusion in the study. All experiments were performed in accordance with relevant guidelines and regulations.

2.2 MRI acquisition and processing

All University of Minnesota participants were scanned at the Center for Magnetic Resonance Research on a 7T-Terra MRI scanner using SC72 gradients capable of 70 mT/m and a 200 T/m/s slew rate, driven by a Siemens console (Erlangen, Germany). The images were acquired with a 32-element head array coil (Nova Medical, Inc, Burlington, MA). Diffusion-weighted images covering the whole brain were acquired using 50 directions, b-value = 1,500 s/mm^2, 4 additional b0-volumes, 1.25 mm isotropic voxels, multi-band (MB) = 2, parallel acceleration (GRAPPA) = 2. The diffusion images were acquired twice, each with different phase encoding directions: anterior-posterior and posterior-anterior for a total of 13 minutes. Additionally, for our control participant, an additional session included an FGATIR (whole-brain, 0.8 mm isotropic, TR/TE = 3,000/2ms, TI = 430ms, GRAPPA = 2, 8 min 43 s), SWI (0.4x0.4x08 mm interpolated to 0.2x0.2x0.8 mm, TR/TE = 210/14ms, GRAPPA = 2, 7 min 33 s), and a multi-echo MP2RAGE in order to generate a synthetic WMn-MPRAGE image to obtain the THOMAS atlas output (Su et al., 2019) (0.66 mm isotropic, TR = 6,000 ms, TE = 1.8/3.6/5.5/7.4 ms, TI = 750/2950 ms, GRAPPA = 3, 12 min 20 s).

dMRI preprocessing steps included: motion, susceptibility, and eddy current distortions correction using FSL's eddy and topup algorithms (Andersson et al., 2003). The DiMANI images were generated by computing the mean, voxelwise, of the diffusion weighted volumes (e.g., only b > 100 volumes were kept). For visualization purposes, DiMANI images were equalized using an adaptive histogram equalization (https://github.com/VincentStimper/mclahe).

The HCP datasets were acquired at 3T and 7T. The protocols have been published elsewhere (Sotiropoulos et al., 2013, 2016; Moeller et al., 2021). The 3T HCP diffusion MRI dataset was acquired at 1.25 mm isotropic resolution with 3 shells (b = 1,000, 2,000, 3,000 s/mm^2) and a total of 288 diffusion volumes (18 b-0 volumes). The 7T HCP diffusion dataset was acquired at 1 mm isotropic resolution with 2 shells (b = 1,000 and 2,000 s/mm^2) and a total of 143 directions (15 b-0 volumes). The PPMI dataset was acquired using a 3T MRI scanner with 2 mm isotropic voxels, b = 1,000 s/mm^2 and 64 directions plus one b-0 volume. For the HCP and PPMI datasets, the downloaded datasets were already processed.

2.3 Thalamus segmentation

Manual segmentation of the thalamus and its subnuclei was carried out using the contrast information from the average diffusion image of each participant separately. There is a wide variety of thalamic subnuclei nomenclature and subdivisions in the literature arising from differences in the methodology used to visualize the thalamus. Therefore, we could not conduct segmentation of the subnuclei following all available atlases. The THOMAS atlas is arguably the current gold standard for thalamic subnuclei subdivision using MRI (Su et al., 2019). One advantage of using this atlas is its distribution with code that enables automatic parcellation of the thalamus based on the subject's images. This facilitates comparison of our manual segmentations to a state-of-the-art tool. Its nomenclature and subdivision are largely based on that of the Morel atlas (Morel et al., 1997). The Morel atlas contains many more subnuclei than the THOMAS because it is based on histology, rather than MRI which has much lower resolution. In this study, we will show results based on both atlases and nomenclatures. The THOMAS atlas subnuclei segmentations come from the output of the inference code (https://github.com/thalamicseg/thomas_new) based on a participant synthetic WMn-MPRAGE computed from the multi-echo MP2RAGE image (Su et al., 2019). The Morel atlas was non-linearly warped to the subject's native space using the HCP pipelines (FSL FLIRT and FNIRT) (Glasser et al., 2013).

2.4 Reproducibility of the visualization

One healthy control was scanned 8 times over the course of 26 months on two different 7T MRI scanners at the University of Minnesota (Siemens MAGNETOM actively shielded and Siemens

MAGNETOM 7T Terra) employing similar acquisition protocols as described above. Manual segmentation was performed on each dataset separately. The resulting segmentations were registered to one of the eight datasets using affine registrations and Dice coefficients (DCs) were computed for each nucleus inside of Slicer3D (Fedorov et al., 2012). Additionally, manual segmentation was performed across three experienced raters independently on five ET patients and an inter-rater DC was also computed.

2.5 Clinical validation

The purpose of this experiment was to verify the accuracy of our manual segmentation of the Vim and its surrounding subnuclei by comparing them with the placement of the DBS electrodes. Additionally, using the surgical notes and the reconstruction of the microelectrode recordings (MER) trajectories, we aimed to verify the segmentation of the ventral posterior lateral (VPL) region [also called Vc (Ilinsky and Kultas-Ilinsky, 2002)]. A typical targeting methodology at our center is to use a "cross-shaped" BenGun affixed to the head frame and aligned in the patient's anterior-posterior direction. MER is then performed in the posterior and center positions and cell firing patterns and receptive fields are identified. VPL cells are recognizable by tactile receptive fields. Distance from the posterior position for lead implantation depends on where Vc is identified. Roughly 4 weeks post-surgery, a postop computed tomography (CT) image is acquired, and the DBS system is turned on and optimized for patient benefits against side effects.

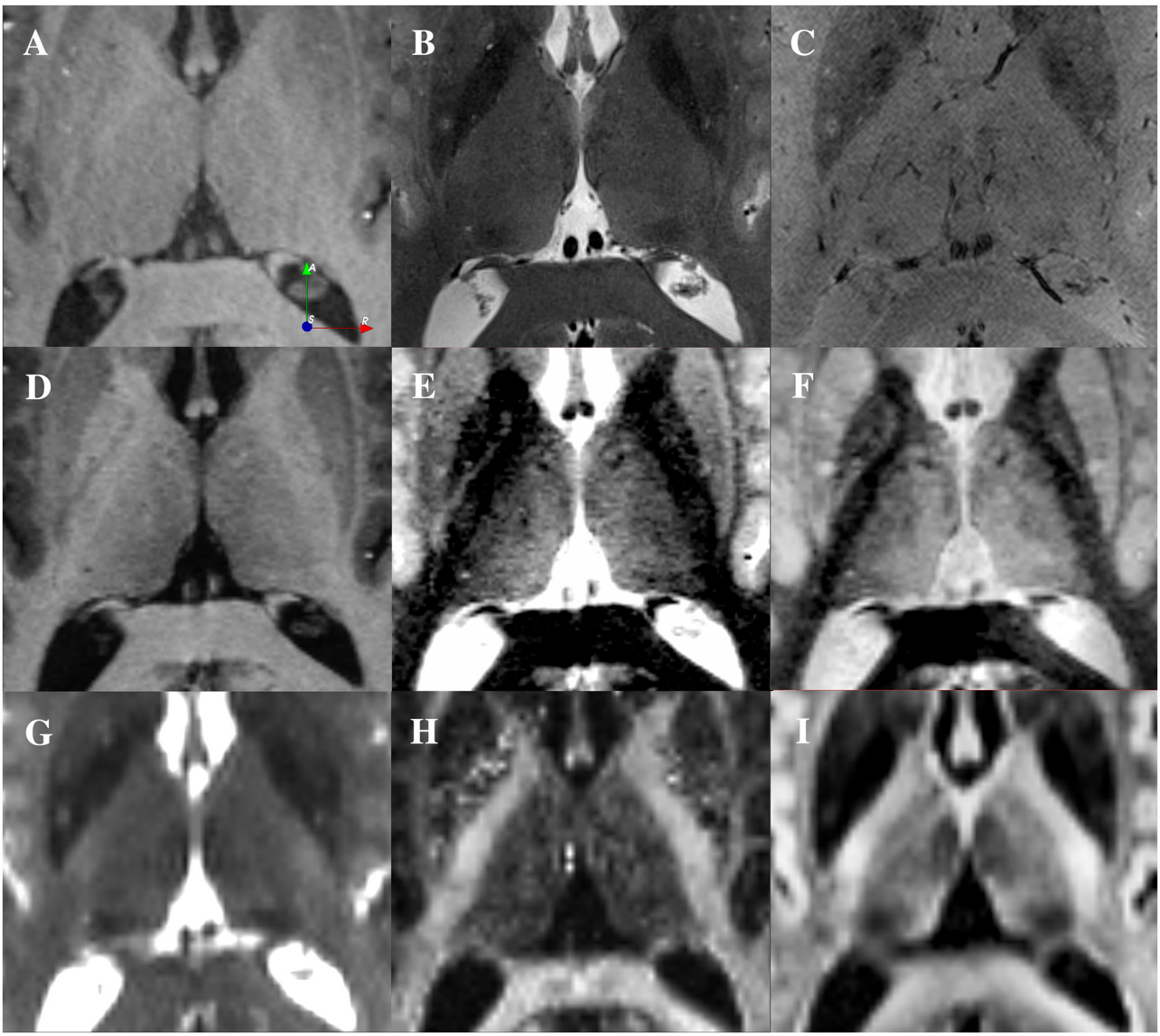

FIGURE 1
Visualization of the thalamus using different contrasts at 7T from a single participant. **(A)** T1-weighted image (0.6 mm isotropic). **(B)** T2-weighted image (0.4x0.4x1 mm). **(C)** SWI image (0.4x0.4x0.8 mm). **(D)** Multi-echo MP2RAGE (0.7 mm isotropic). **(E)** Synthetic WMn-MPRAGE reconstructed from the multi-echo MP2RAGE (0.7 mm isotropic). **(F)** FGATIR image (0.8 mm isotropic). **(G)** Average across 4 B0 images from a dMRI dataset (1.25 mm isotropic). **(H)** Fractional Anisotropy computed the dMRI data (1.25 mm isotropic). **(I)** DiMANI image reconstructed from the dMRI dataset (1.25 mm isotropic).

The CT is then non-linearly registered to the MR images using Elastix (Klein et al., 2010) in order to locate the exact location of the DBS electrode (s) (shaft and contacts) within the patient's own anatomy. Additionally, we extract the depths at which VPL cells were identified intra-operatively and map them in 3D with respect to the final lead location using 3D Slicer (Fedorov et al., 2012).

2.6 DTI and tractography validation

The purpose of this qualitative experiment is to verify the accuracy of our manual segmentations against probabilistic and deterministic tractography results. Following dyads computation using bedpostx, probtrackx2 (Behrens et al., 2003) (with the –os2t option) was used to generate probabilistic tractography maps with each thalamus as a seed and cortical regions as targets. The cortical targets were: M1, S1, premotor, supplemental motor area (SMA), limbic, associative, parietal, occipital, and temporal. This resulted in one thalamus map per ipsilateral cortical target (9 per side). Each map was thresholded to its 99th percentile to find the thalamic location of highest connectivity to each cortical region. This location was overlaid on the manual segmentation. For the deterministic experiment, the preprocessed data were imported into DSI studio (http://dsi-studio.labsolver.org) along with the manual segmentations. A deterministic fiber tracking algorithm (Yeh et al., 2013) was used with augmented tracking strategies (Yeh, 2020) to improve reproducibility. Each manually segmented thalamic nucleus was used as a seed with the other regions set as regions of avoidance, with the exception of the intralaminar subnuclei for which no regions of avoidance were set. Additionally, a mid-sagittal plane was created from the bottom of the thalamus to the top of the cortex and used as a region of avoidance to minimize cross-hemispheric streamlines. Tracking was stopped once 5,000 streamlines were created. Tracks with lengths shorter than 50 or longer than 150 mm were discarded. Other parameters were set to default.

3 Results

3.1 Nucleus visualization

Panels of Figure 1 display one axial slice, from a single participant, through the thalamus for MRI contrasts commonly

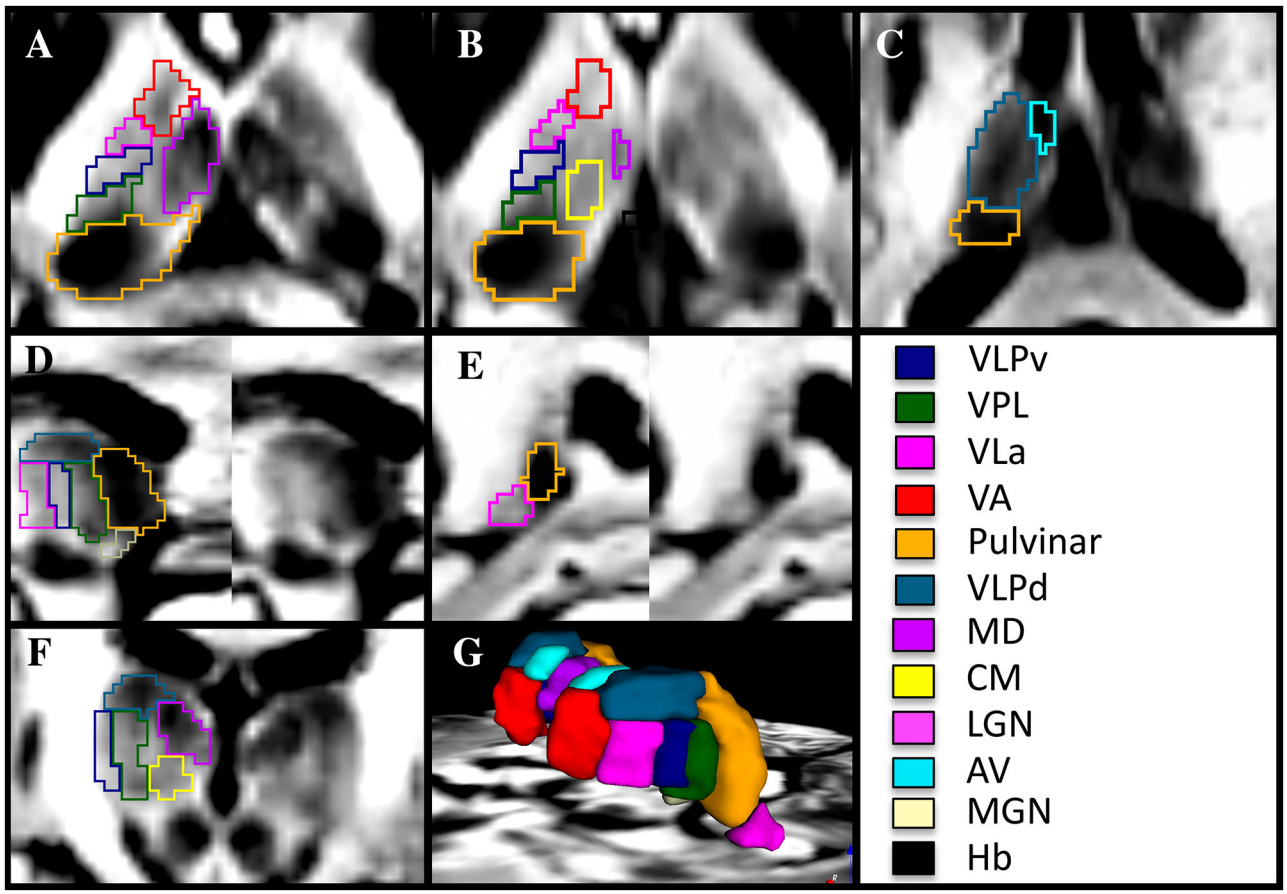

FIGURE 2
Manual segmentation of thalamic subnuclei using a 7T DiMANI image following conventions from the THOMAS atlas in axial **(A–C)**, sagittal **(D, E)**, coronal **(F)**, and in 3D **(G)** in a healthy volunteer. VLPv, ventral portion of the ventral lateral posterior nucleus; VLPd, dorsal portion of the ventral lateral posterior nucleus; VPL, Ventral posterior lateral nucleus; VLa, Ventral lateral anterior nucleus; VA, Ventral anterior nucleus; MD, Mediodorsal nucleus; CM, Centromedian nucleus; LGN, Lateral geniculate nucleus; AV, Anterior ventral nucleus; MGN, Medial geniculate nucleus; Hb, Habenular nucleus.

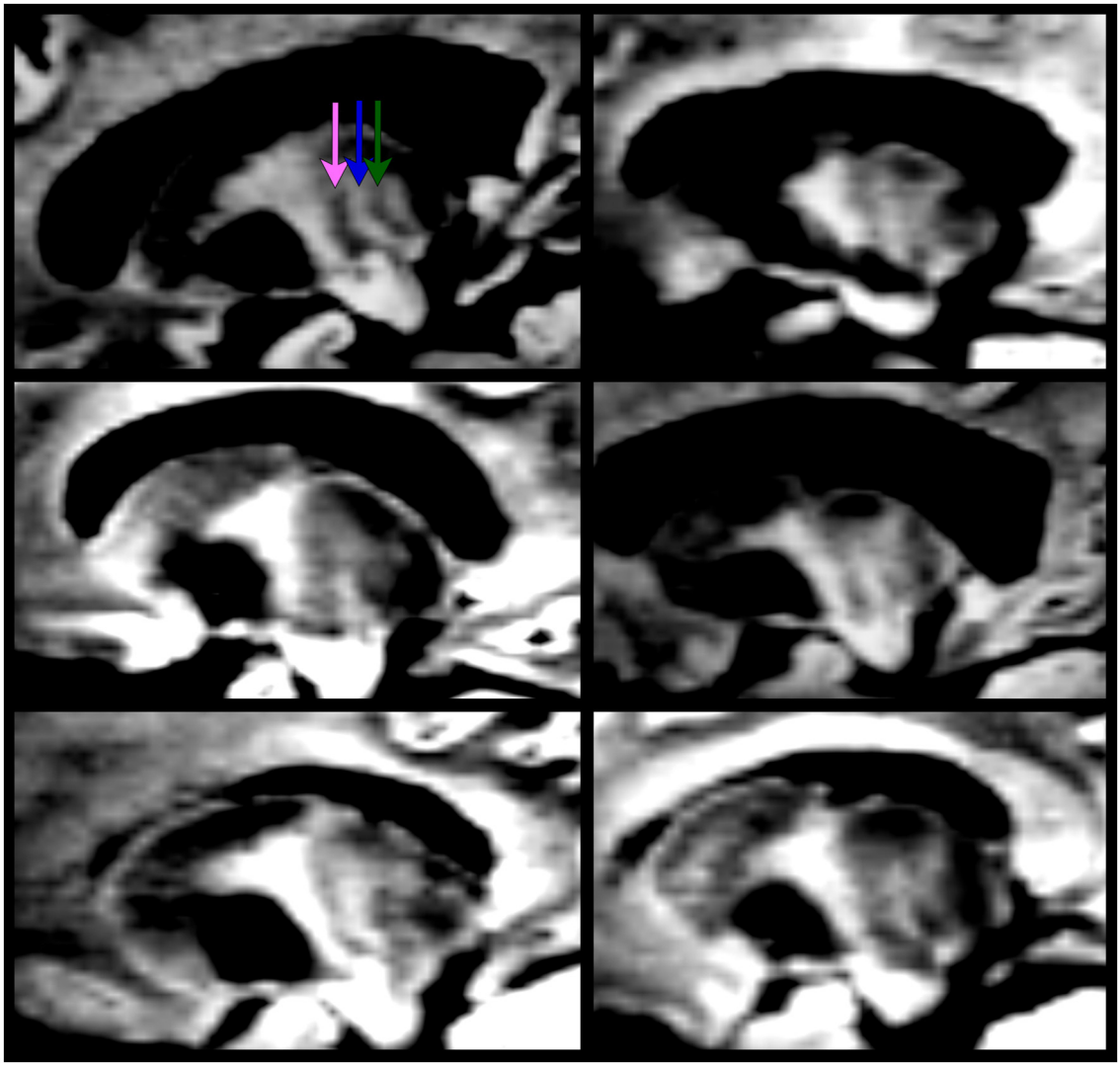

FIGURE 3
The "zebra pattern" is present in all ET patients enrolled in this study (using the 7T DiMANI image). The pink arrow represents the location of VLa; the blue arrow, VLPv; the green arrow, VPL.

used to visualize the thalamus. On the T1 and T2 weighted and fractional anisotropy (FA) images (obtained with dtifit), little to no detail is visible within the structure (Figures 1A, B, H, respectively). The B0 image (Figure 1G) shows more information, especially for the MD and posteriormost regions of the thalamus (pulvinar and VPL). The FGATIR and WMn-MPRAGE images show details in the lateral and anterior portions of the thalamus (Figures 1F, E). However, while the center of mass of some subnuclei can be inferred, most of these images do not enable reliable visualization of the borders of most subnuclei as described in atlases such as THOMAS and Morel.

In contrast to the common MRI protocols that exhibit relatively flat or minimal details (Figure 1), the DiMANI method provides enhanced dynamic range and enables direct visualization of thalamic subnuclei (Figure 1I), including their borders, as seen in Figures 2A–F.

The optimal view for manually segmenting subnuclei depends on the specific subnuclei being segmented. For example, the sagittal orientation proved key in segmenting the VLa, VLPv, and VPL as stripes of alternating dark and bright signals forming a "zebra pattern" were observed. This "zebra pattern" was visible on all our participants, including across ET patients (Figure 3).

The VLPd appears as a dark structure separated from the VLPv, VLa, and VPL in the coronal and sagittal views. The MD, appearing very dark, is visible and separated in all orientations from its bright to light gray surroundings, which are comprised of the internal medullary lamina laterally, the stria medullaris medially and ventral regions including the CM (ventral lateral). The separation between MD and CM is most visible in the coronal view. The pulvinar, darker than the VPL located at its anterior border, is best segmented in the axial view and corrected in the sagittal view. The anteriormost part of the VA

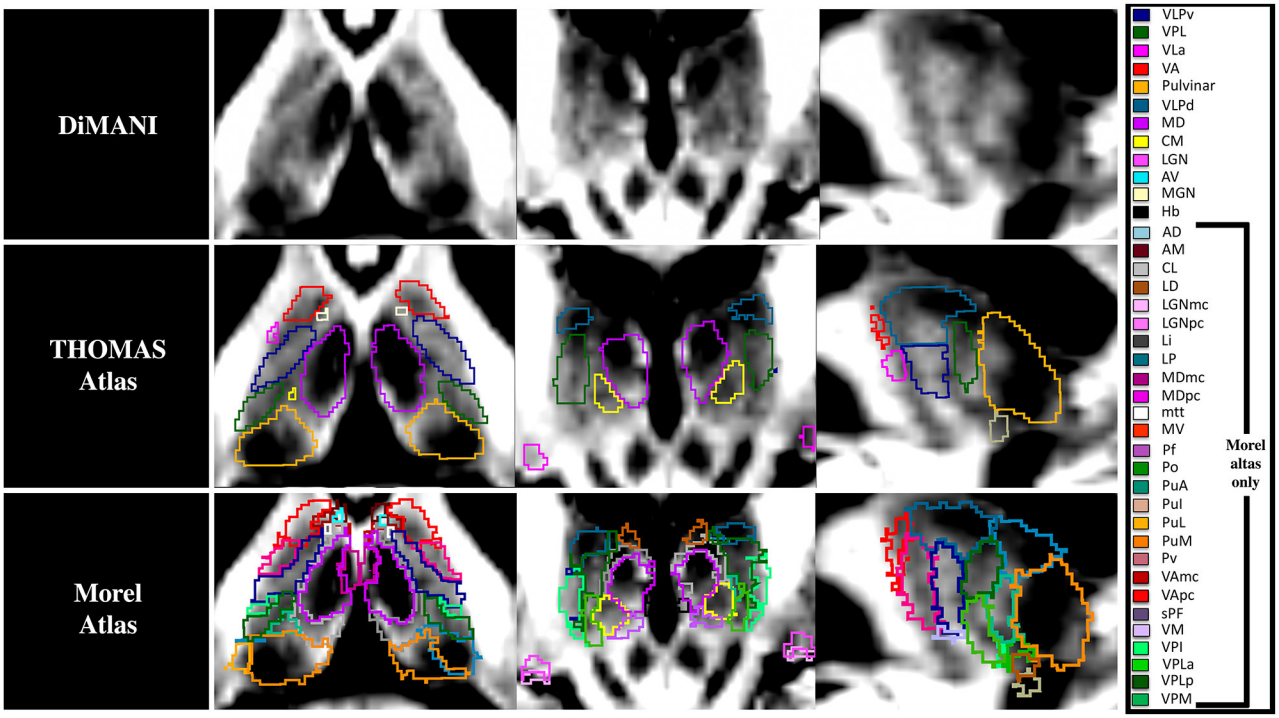

FIGURE 4
The DiMANI contrast obtained at 7T shows information that follows known anatomical organization from common atlases. All abbreviations are based on the Morel atlas (Morel et al., 1997).

is segmented in the coronal view while its borders with the lighter internal medullary lamina and dark VLa are segmented in the axial view. The very dark AV, situated at the most dorsal anterior and medial portion of the thalamus, is segmented in the axial and coronal views. The Hb is very small and is better visualized in the axial and coronal views. The lateral and medial geniculate subnuclei are both lighter than their shared neighbor, the pulvinar. It should be noted here that the MTT was not visible in all slices, hence manual segmentation of this white matter structure was not performed. This is likely due to image resolution (1.25 mm isotropic) with respect to the shape and volume of the structure.

Figure 4 shows that the DiMANI contrast corresponds to the overall organization of the THOMAS and Morel atlases (results are overlayed on the DiMANI image). Of note, the DiMANI contrast also enables visualization of subnuclei present in the Morel atlas but not in the THOMAS atlas. Of the many additional subnuclei, we were able to identify structures that likely correspond to the CL, PuA, LP, VPM, VPI, MDmc, MDpc, LGNmc, LGNpc, Pf, and sPF subnuclei.

3.2 Reproducibility

To test the reliability of the segmentations based on the DiMANI contrast we calculated the overlap between manual segmentations performed on 8 scans of the same individual. Figure 5A shows the Dice coefficients (DCs) for the manual segmentation of the twelve visible subnuclei following the THOMAS atlas as a guide. This resulted in fourteen DCs per subnuclei (seven left and right). The averaged DCs were all between 0.62 and 0.85 except for the small Hb nucleus (DC = 0.50). Figure 5B shows the results for the inter-rater reliability. Each of the twelve subnuclei were segmented independently by three raters yielding in 120 manual segmentations per rater (12[subnuclei] x 2[sides] x 5[patients]). This resulted in comparable DCs to those obtained from the test-retest analysis (average DCs ranging from 0.46 to 0.81).

3.3 Clinical and imaging validation

The goal of any new method is to provide added value to clinical and research approaches. Here, we show that the DiMANI contrast allows the segmentations and creation of 3D patient-specific models that depict the location of thalamic subnuclei. We leveraged neurophysiological data to test the validity of the DiMANI-based models by correlating the locations of the DBS electrodes and the stimulating contacts with the target subnuclei. Figure 6 shows that all nine active DBS contacts were at or near the VLPv-VLa border, which is consistent with expected lead locations based on our center's targeting approach.

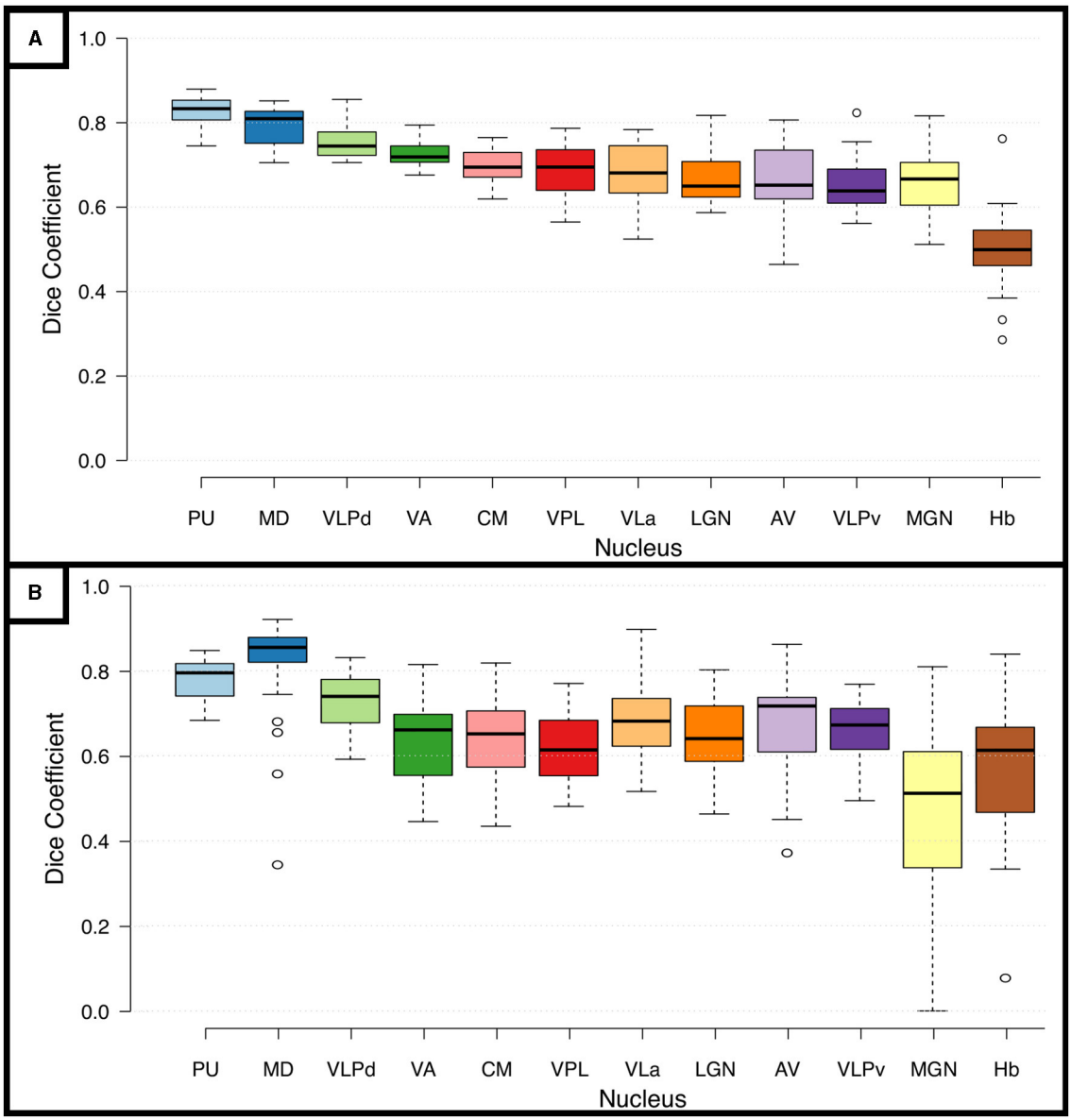

FIGURE 5
Reproducibility and Reliability of the manual segmentations using the DiMANI contrast. **(A)** Shows the dice coefficients from the manual segmentations performed on eight scans from the same participant. **(B)** Shows the inter-rater dice coefficients computed from manual segmentations of 5 patients from three raters (totaling 30 DC per subnuclei: 5patients x 2 hemispheres x 3 rater combinations).

Additionally, 11 of 12 MER tracks displaying activity interpreted as VPL cells overlapped fully with the manual segmentations of the VPL. The twelfth was found just anterior to VPL within VLPv.

Figure 7 shows that both probabilistic and deterministic tractography result in known connections between the manual segmentations and cortical regions. For example, the VLPv connects to M1, the VPL to S1, the LGN to visual areas, and the VLa to premotor and SMA regions. Additionally, some of the thalamic regions show different fiber orientations compared to their neighbors, as expected from local fiber orientation parcellation methods (Figure 7C).

3.4 Impact of acquisition parameters

Figure 8 shows the DiMANI contrast using different numbers of diffusion gradient directions from the same dataset. In our original data, we used 50 directions. However, the DiMANI contrast enables direct visualization of thalamic subnuclei even with a smaller number of directions. The main difference is the image noise level.

Figure 9 shows that many of the subnuclei are visible with the DiMANI contrast at two field strengths, different resolutions, and acquisition parameters. Both HCP datasets, coming from the same subject but at different field strengths, show repeatable features

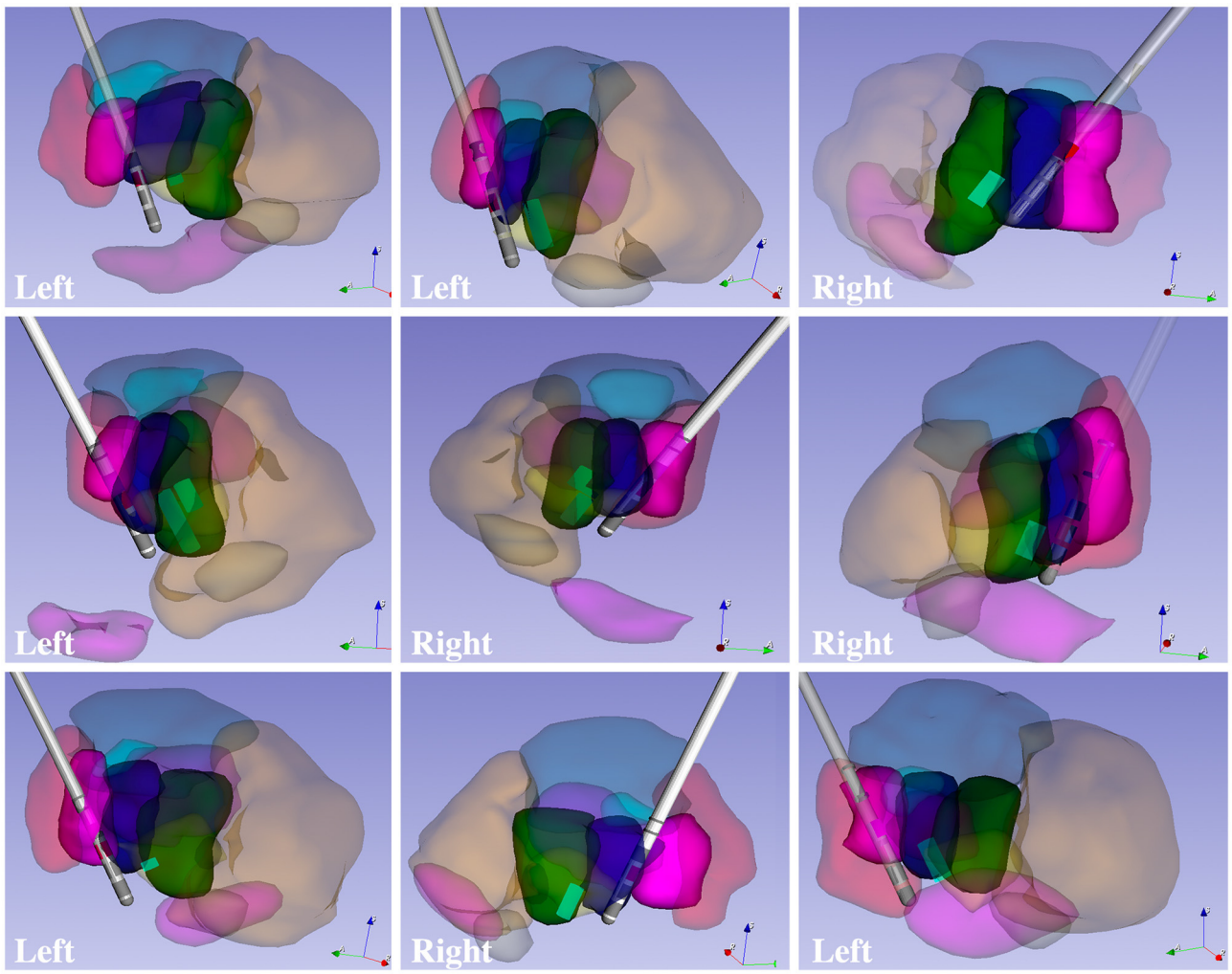

FIGURE 6
3D models of patient-specific thalamic segmentations combined with DBS lead and VPL cell locations for six patients totaling nine leads.

akin to those seen with the UMN data. The PPMI image, despite being acquired at 3T and being lower resolution, still enables the visualization of the zebra pattern in the sagittal view and several subnuclei in the axial.

4 Discussion

Here we present a new method for enhancing the anatomical contrast of subcortical tissue. The DiMANI method is based on averaging diffusion-weighted volumes, which allows one to directly visualize the subnuclei of the thalamus. Diffusion-based segmentation is becoming a field of interest as it enables faster acquisition of diffusion-related metrics for specific structures without relying on registration to a T1 or another modality. Few other studies have used a similar diffusion-based contrast to DiMANI; however, they focused on segmenting brain lesions (Liu et al., 2021), the gray matter ribbon (Little and Beaulieu, 2021), or the classic three-tissue type segmentation (white matter, gray matter, and cerebrospinal fluid) (Cheng et al., 2020). Although most current dMRI-based segmentation studies use state-of-the-art neural network technology, they are limited to the classical three-tissue based segmentation due to their use of common dMRI maps such as tensor and kurtosis results (Ciritsis et al., 2018; Cheng et al., 2020; Wang et al., 2020; Little and Beaulieu, 2021; Zhang et al., 2021). One other study created a deep learning algorithm to segment ten brain structures using dMRI data, but their ground truth was not based on segmentation from the dMRI data but rather warped atlas into diffusion space (Theaud et al., 2022). Due to the level of details exhibited, the DiMANI method has the potential to be used to generate gold standard ground truth for diffusion-based segmentation methods and improve current neural network approaches based on dMRI.

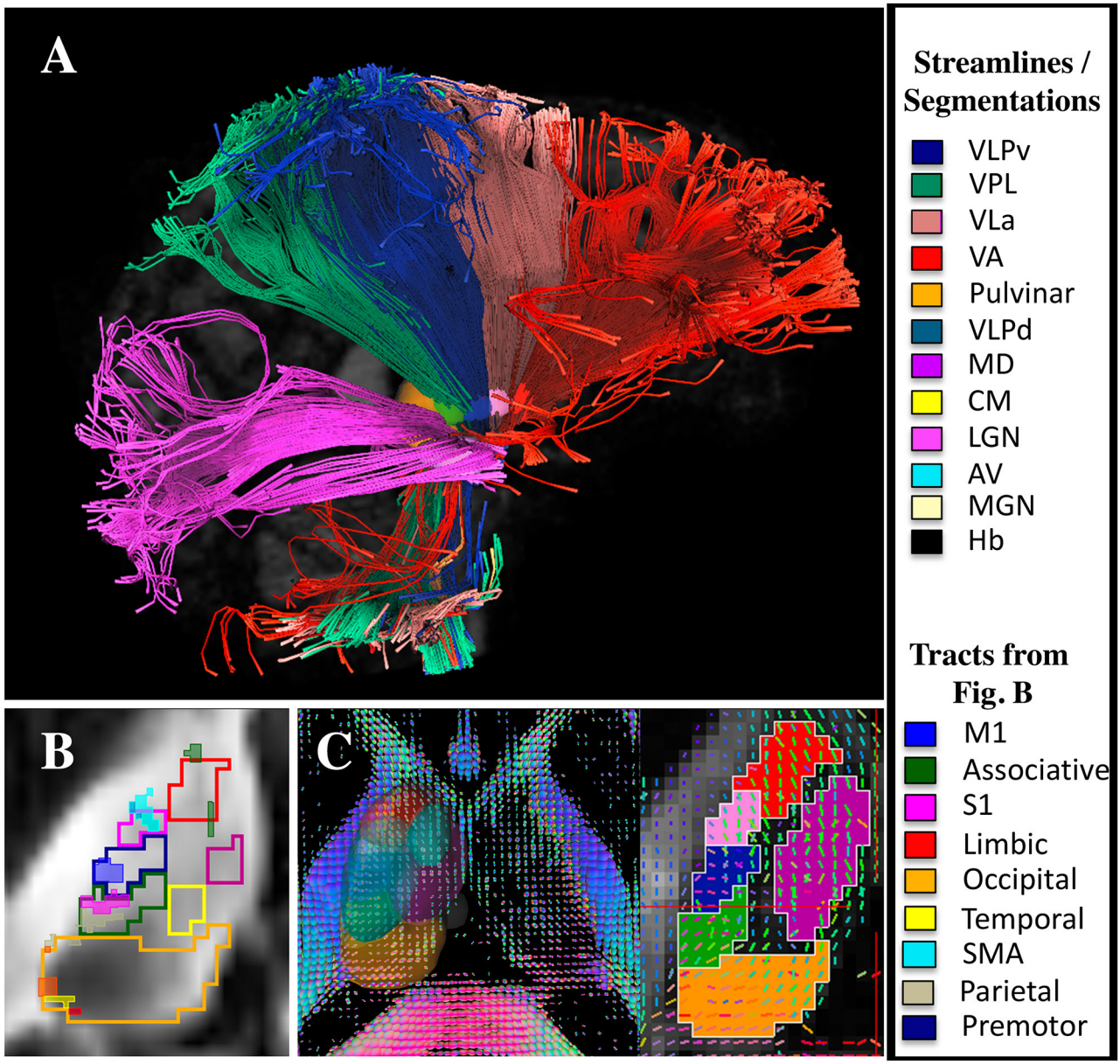

FIGURE 7
DTI and tractography validation. **(A)** Deterministic tractography results from the LGN, VPL, VLPv, VLa, and VA regions (note that the tractography was performed without cortical parcellations). **(B)** Probabilistic tractography results showing the connectivity hotspots (thresholded at 99% of the distribution) between cortical regions and the thalamus overlaid on manual segmentations performed using the DiMANI contrast (note that the tractography was performed without the manual segmentations). **(C)** Manual segmentations overlaid on local fiber orientation computed with DSI studio.

4.1 DiMANI contrast

In the DiMANI contrast, regions exhibiting dark signals are regions where water can diffuse isotropically (e.g., CSF) while bright regions reflect highly constrained water movement, or anisotropic diffusion (e.g., white matter tracts). The images from the present study show consistently and reliably different thalamic subnuclei with different levels of average diffusion signals reflecting the underlying histology of these subnuclei (Figures 2–4). Note that 50 directions randomly covering q-space (Caruyer et al., 2013) were averaged; therefore, it is unlikely that the contrast difference between any two subnuclei is due to any specific directions contained in the b-vectors. Further, we have shown that multiple datasets, using their own b-vector table, displayed similar DiMANI contrasts (Figure 9). The DiMANI contrast was also reliable (Figure 5A) and several raters were able to segment the subnuclei consistently (Figure 5B). Finally, the contrast was observed at multiple field strengths (Figure 9). It should be noted that different mathematical operations [mean, median, centromean (mean of middle 50% values), sum and the l2norm]

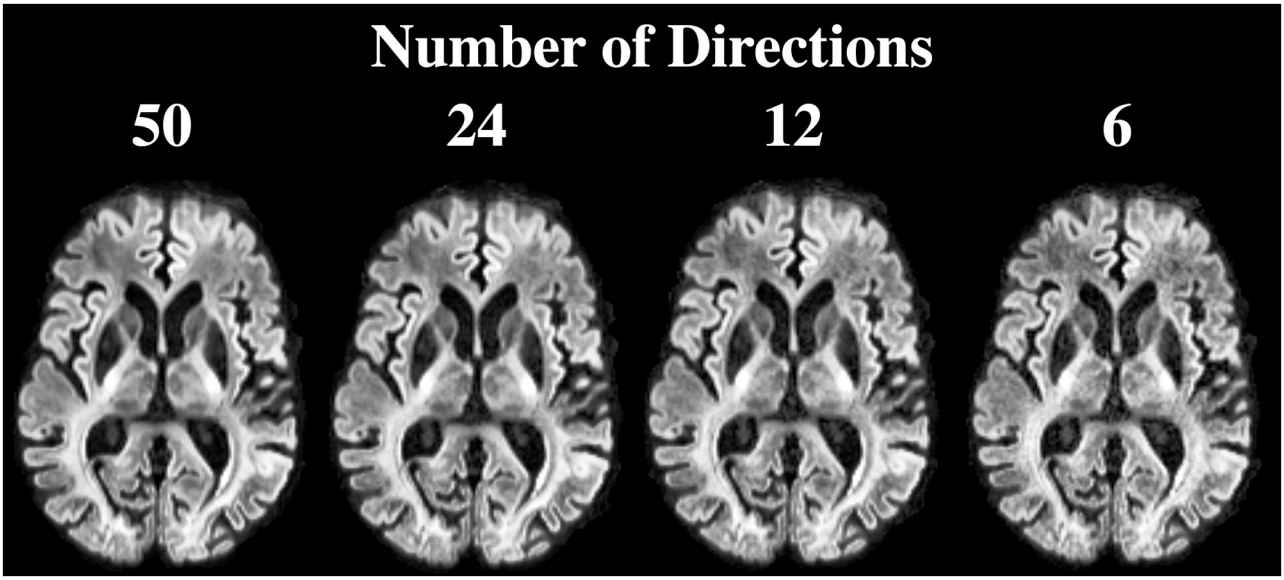

FIGURE 8
DiMANI contrast obtained using different numbers of directions and $b = 1{,}500$ s/mm^2. Each dataset samples q-space uniformly.

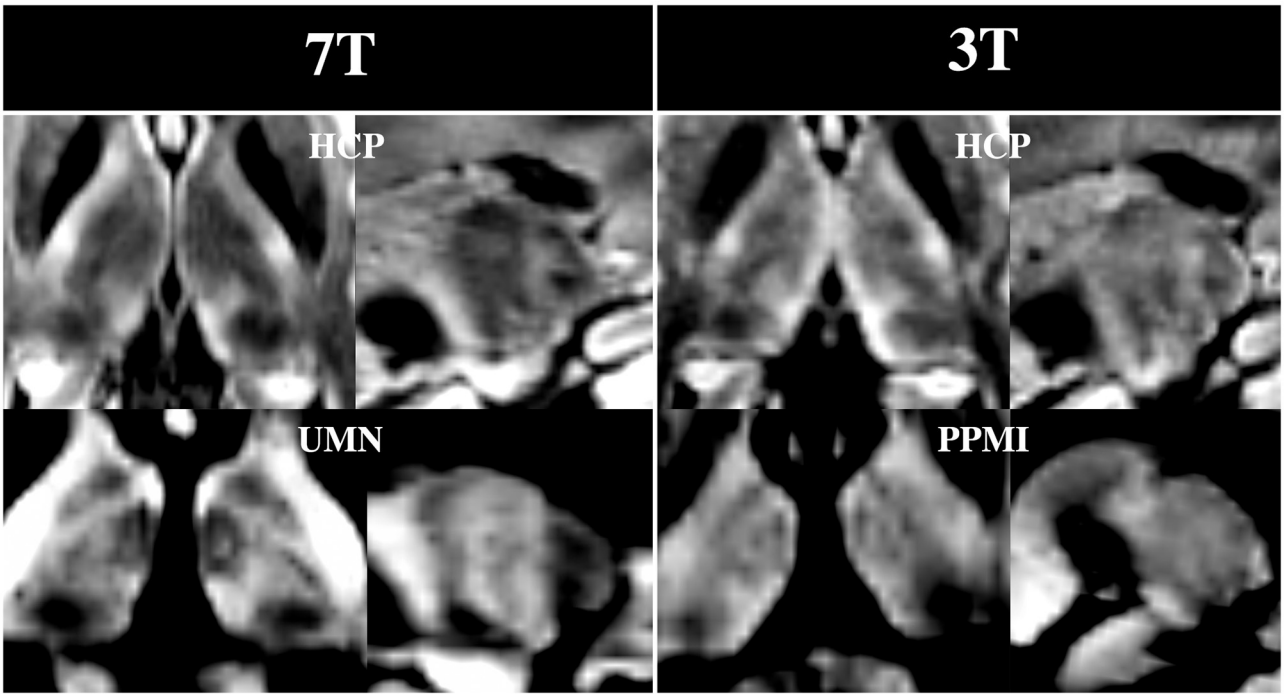

FIGURE 9
DiMANI images from multiple databases. Note that both HCP images were from dMRI sets acquired from the same control subject and shown for the $b = 1{,}000$ s/mm^2 shell.

yield similar contrasts with only few slight visual variations in in terms of noise and brightness; voxel values did differ across these different methods, but the visual contrast did not. In this study we chose the mean as this contrast is commonly used in DWI methods papers (Lee et al., 2021; Feizollah and Tardif, 2023).

4.2 Research potential

As shown in Figures 8, 9, the DiMANI contrast enables direct visualization of thalamic subnuclei with a variety of acquisition methods and parameters. This offers a clear advantage over methods that require the use of new sequences and

the acquisition of new data. It enables researchers who have previously collected data to utilize this approach for thalamic parcellation. Further, a large number of ongoing neuroimaging studies already acquire dMRI data and no change of protocol would be required for these research teams to implement DiMANI in their pipeline. Additionally, using the DiMANI contrast to directly visualize and segment thalamic subnuclei facilitates the execution of diffusion-based research projects since no registration to other modalities or templates is necessary. Further, by eliminating registration errors and performing subject-specific segmentation, the accuracy of the representation of the anatomy is improved, thereby yielding more precise results when looking at quantitative diffusion metrics within specific subnuclei across groups.

4.3 Translational potential

We have shown in this work that thalamic subnuclei are directly visible in healthy controls as well as movement disorder patients using 7T and 3T, two field strengths currently FDA and CE approved for clinical work (Figure 9). Additionally, while having more diffusion directions clearly helps attain the appropriate signal-to-noise ratio (SNR), we have shown that usable results can be achieved with a smaller number of directions, which is more reasonable for a clinical setting (Figure 9). For thalamic-based therapies, such as DBS and focused ultrasound, direct visualization of the subnuclei could aid the targeting process by providing patient-specific information and enabling direct targeting (e.g., Vim for ET, anterior thalamus for epilepsy). Accurate direct targeting of thalamic subnuclei has the potential to reduce the heterogeneity in treatment outcome. Additionally, the ability to visualize the DBS electrodes with respect to the patient's actual anatomy could help clinicians decipher optimal stimulation settings more efficiently and provide context to the presence of side effects at lower thresholds in some patients. Further, the DiMANI contrast could potentially help identifying which thalamic subnuclei are affected when irregular thalamic anatomy such as atrophy or lesions are present. The method of averaging the diffusion weighted volumes is simple and is similar to "isotropic DWI" in the field of Radiology, a contrast that many scanners can generate. Therefore, there is no technical limitation for vendors to implement such contrast. The DiMANI method presented here is not proposed to replace existing methods, such as FGATIR. Instead, it is meant to be an additional tool available to directly visualize these elusive structures.

4.4 Limitations

One limitation worth noting is that DWI uses echo planar imaging (EPI-based) sequences which exhibit larger geometric distortions and susceptibility artifacts in the phase encoding direction. These are mainly problematic for surgical applications, such as pre-surgical planning for DBS and focused ultrasound. In our work, we acquired the diffusion data twice in a "blip up, blip down" configuration and processed the images using topup to mitigate this issue. The region of the thalamus, due to its central location, is less impacted by these distortions and as such the impact should be minimal compared to the cortex. One solution might be the use of multi-shot echoplanar diffusion MRI sequences that promise to result in sharper and largely distortion-free images, such as the FDA-approved syngo RESOLVE (https://www.siemens-healthineers.com/en-us/magnetic-resonance-imaging/options-and-upgrades/clinical-applications/syngo-resolve). Other solutions include gSlider BUDA-EPI and multi-coil dynamic B0 shimming (Liao et al., 2021) and MUSE (Chen et al., 2013). However, this does require longer acquisition times. While we have run this dMRI acquisition protocol on more than 100 DBS patients at 7T, we understand that acquiring about 13 min of dMRI data can be difficult in some patients. Future work will focus on optimizing DiMANI acquisition at 3T and 7T such that protocols could be seamlessly implemented in the clinic even in centers without a 7T scanner.

Manually segmenting a dozen or more subnuclei for every individual is extremely time consuming and potentially unfeasible. This is not problematic for clinical work since surgical teams only need to know the location of one or a few subnuclei depending on the application. For research, however, future work should focus on training deep learning algorithms specific to the DiMANI contrast to eliminate the need for manual segmentation. Finally, while the dMRI datasets presented here can be considered high resolution (1–1.25 mm isotropic), they are likely not able to resolve some of the smallest subnuclei found in histology and staining reports. Therefore, future studies should focus on acquiring higher resolution (sub-millimeter) dMRI data to uncover whether using DiMANI can enable direct visualization of more of the smaller subnuclei. Additionally, future work should focus on studying the impact of denoising tools on the DiMANI contrast and whether these tools can enable further optimization of data acquisition. Finally, follow-up studies should also evaluate whether the DiMANI contrast is able to depict variability in the size, shape and location of thalamic subnuclei among healthy subjects as well as those and in the diseased condition.

5 Conclusion

This study introduces the DiMANI contrast to directly visualize thalamic subnuclei using diffusion-weighted imaging. We have shown that this contrast is reliable and has a multitude of potential applications. DiMANI has great research potential as it can be applied to various acquisition methods and parameters, allowing researchers to utilize existing data to study the thalamus. Its direct visualization and segmentation capabilities eliminate the need for registration to other modalities, facilitating diffusion-based research projects. The translation to clinical applications of the DiMANI method may have significant impact as direct visualization of thalamic subnuclei can assist in the targeting and optimizations of thalamic-based neuromodulation therapies. In conclusion, this relatively simple method shows promising prospects and could be useful to the research and clinical community alike.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Minnesota Internal Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. TP: Data curation, Formal analysis, Investigation, Project administration, Software, Validation, Writing – review & editing. JC: Formal analysis, Investigation, Software, Validation, Writing – review & editing. KS: Investigation, Writing – review & editing. HB: Methodology, Software, Writing – review & editing. EY: Methodology, Writing – review & editing. RM: Investigation, Writing – review & editing. JA: Investigation, Writing – review & editing. SC: Investigation, Writing – review & editing. JV: Investigation, Writing – review & editing, Funding acquisition, Supervision. NH: Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

RP is a consultant for Surgical Information Sciences, Inc. TP has been a consultant for Surgical Information Sciences, Inc. JV has received consulting fees from Abbott, Adamas, Boston Scientific, Insightec, LivaNova, Cala Health and Medtronic. He has received research grants from Boston Scientific, Medtronic, NIH, and St Jude Medical. He is on the executive advisory board for Abbott and serves on the Scientific Advisory Board for Surgical Information Sciences. JA is a consultant for Surgical Information Sciences, Inc. NH is a co-founder of Surgical Information Sciences, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2024.1324710/full#supplementary-material

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Proceedings of the 11th Annual Deep Brain Stimulation Think Tank: pushing the forefront of neuromodulation with functional network mapping, biomarkers for adaptive DBS, bioethical dilemmas, AI-guided neuromodulation, and translational advancements

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The Deep Brain Stimulation (DBS) Think Tank XI was held on August 9–11, 2023 in Gainesville, Florida with the theme of "Pushing the Forefront of Neuromodulation". The keynote speaker was Dr. Nico Dosenbach from Washington University in St. Louis, Missouri. He presented his research recently published in Nature inn a collaboration with Dr. Evan Gordon to identify and characterize the somato-cognitive action network (SCAN), which has redefined the motor homunculus and has led to new hypotheses about the integrative networks underpinning therapeutic DBS. The DBS Think Tank was founded in 2012 and provides an open platform where clinicians, engineers, and researchers (from industry and academia) can freely discuss current and emerging DBS technologies, as well as logistical and ethical issues facing the field. The group estimated that globally more than 263,000 DBS devices have been implanted for neurological and neuropsychiatric disorders. This year's meeting was focused on advances in the following areas: cutting-edge translational neuromodulation, cutting-edge physiology, advances in neuromodulation from Europe and Asia, neuroethical dilemmas, artificial intelligence and computational modeling, time scales in DBS for mood disorders, and advances in future neuromodulation devices.

KEYWORDS

deep brain stimulation (DBS), artificial intelligence, neuroethics, interventional psychiatry, adaptive DBS, Parkinson's disease, epilepsy, optogenetics

Introduction

The 11th Annual Deep Brain Stimulation (DBS) Think Tank meeting was held on August 9–11, 2023 at the University of Florida in Gainesville, Florida and virtually for those not attending in-person (Zoom Video Communications). There have now been an estimated 263,000 DBS devices implanted for neurological and neuropsychiatric disorders worldwide. The DBS Think Tank was founded in 2012 and provides an open platform where clinicians, engineers, and researchers (from industry and academia) can freely discuss current and emerging DBS technologies, as well as logistical and ethical issues facing the field. The DBS Think Tank emphasizes cutting-edge research and collaboration, aiming to more rapidly advance the neuromodulation field.

The DBS Think Tank meeting was focused on advances in the following areas:

1. Cutting-edge translational neuromodulation, including optogenetics and vagus nerve stimulation;
2. Neurophysiology to guide adaptive DBS (aDBS) and to identify neural biomarkers of mood;
3. DBS research in Europe and Asia focused on neurophysiology, sleep, gait, and neuropsychiatry (depression and Tourette syndrome);

4. Neuroethical dilemmas that will likely inform the future of neuromodulation;
5. Cutting-edge artificial intelligence (AI) and computational modeling;
6. Time scales to measure and treat mood disorders with DBS;
7. Critical features to be incorporated in future DBS devices.

These proceedings will summarize the sessions and discussions held at the 11th Annual DBS Think Tank meeting.

The somato-cognitive action network (scan) as a target for neuromodulation

Dr. Nico Dosenbach was the invited keynote speaker, who presented on the story behind his research identifying the somato-cognitive action network (SCAN) together with Dr. Evan Gordon and their collaborative team. They discovered that two parallel systems intertwine in the brain's motor circuits forming an integrate–isolate pattern: effector-specific regions (foot, hand and mouth) for isolating fine motor control and the somato-cognitive action network (SCAN) for integrating goals, physiology, and body movement (Figure 1) (Gordon et al., 2023; Graziano, 2023; Leopold, 2023).

The SCAN regions are strongly functionally connected to each other and to the cingulo-opercular network (CON), which is critical for action (Dosenbach et al., 2006) and physiological control (Pool and Ransohoff, 1949), arousal (Wall and Davis, 1951), errors (Neta et al., 2015), and pain (Hoeppli et al., 2022). In primary motor cortex, concentric effector somatotopies are interrupted by SCAN inter-effector regions. The SCAN inter-effectors lack movement specificity and co-activate during action planning (coordination of hands and feet) and axial body movement (such as of the abdomen or eyebrows).

The SCAN may be directly relevant to advancing neuromodulation. The SCAN includes two thalamic DBS targets: the ventral intermediate (VIM) nucleus for tremor (Ondo et al., 1998; Fasano et al., 2012) and the centromedian (CM) nucleus for epilepsy (Valentín et al., 2013) and Tourette syndrome (Schrock et al., 2015). The anti-tremor effects of the VIM may be mediated by its connectivity to the cerebellum, and the CM's role in arousal may explain its anti-epileptic effects. Additionally, Parkinson's disease (PD) may be related to dysfunction of SCAN circuitry, as PD symptoms cut across motor, physiological and volitional domains [e.g., postural instability, autonomic dysfunction, and reduced self-initiated activity (Dauer and Przedborski, 2003; Bloem et al., 2021)]. Therefore, the SCAN may partially explain the therapeutic effects of DBS in disorders that involve complex motor and nonmotor integration, which could inform novel patient-specific functional mapping for targeted neuromodulation.

Cutting edge translational neuromodulation

Over the past decade, there has been an influx of bench research focused on understanding the therapeutic mechanisms of neuromodulation (Wong et al., 2023). Optogenetics has provided key insights into cell-type specific effects of DBS and developing novel stimulation paradigms for more selective stimulation. Additionally, there is increased interest in understanding the role of learning and neuroplasticity in specific brain circuits in driving motor and nonmotor effects of neuromodulation.

Circuit-inspired strategies to improve treatments for Parkinson's disease

The identification of distinct cell-types throughout the basal ganglia has been essential in advancing the understanding of network function and improving neurological therapies. In the globus pallidus externa (GPe), interventions targeting neuronal subpopulations have profound therapeutic potential, but are challenging to implement in clinical settings. The lab of Dr. Aryn Gittis investigated whether electrical stimulation can be tuned to engage cell-type specific responses in the GPe. Although conventional stimulation was non-specific, brief and high frequency bursts of stimulation elicited bimodal responses of Parvalbumin (PV-GPe) and Lim homeobox 6 (Lhx6-GPe) subpopulations. In dopamine depleted mice, burst-DBS stimulation optimized for cell-type specificity induced motor recovery with sustained therapeutic benefits that persisted for hours after the offset of stimulation. These results establish the feasibility of shaping electrical stimulation patterns to drive population-specific neuromodulation in the central nervous system and suggest a potential for developing a more robust toolbox for DBS therapies in humans.

Modulating neural reinforcement with subthalamic DBS in Parkinson's disease

aDBS provides an unprecedented temporal precision that holds promise to counteract the negative effects of dopamine loss in PD (Neumann et al., 2023a). To achieve this goal, it is crucial to understand the neural circuit dynamics, their function, and their modulation that underlie physiological dopamine signaling. It was recently proposed that the shared effect of dopaminergic signals across limbic, associative, and motor circuits can be neural reinforcement (Athalye et al., 2020), the modulation of strength of neural population dynamics, and their likelihood to reoccur. Translating this concept to PD can spark new hypotheses on the pathogenesis of PD symptoms (Cheung et al., 2023) and ways to counteract them. Given that DBS, like dopamine release, can suppress indirect pathway activity (Neumann et al., 2023b), temporally precise stimulation could mimic the circuit effects of dopamine transients. Early findings from Dr. Julian Neumann's lab support this claim, as kinematic closed-loop DBS shows specific invigorating effects on the behavior at the time during which stimulation is applied. For PD, this could serve as a foundation for neural circuit prosthetics that may reinstate healthy basal ganglia function to counteract pathological reinforcement and support neural learning. If true, this could extend DBS for the adaptation to neuroprosthetics for stroke rehabilitation, spinal cord injury, or retina implants by supporting neural learning.

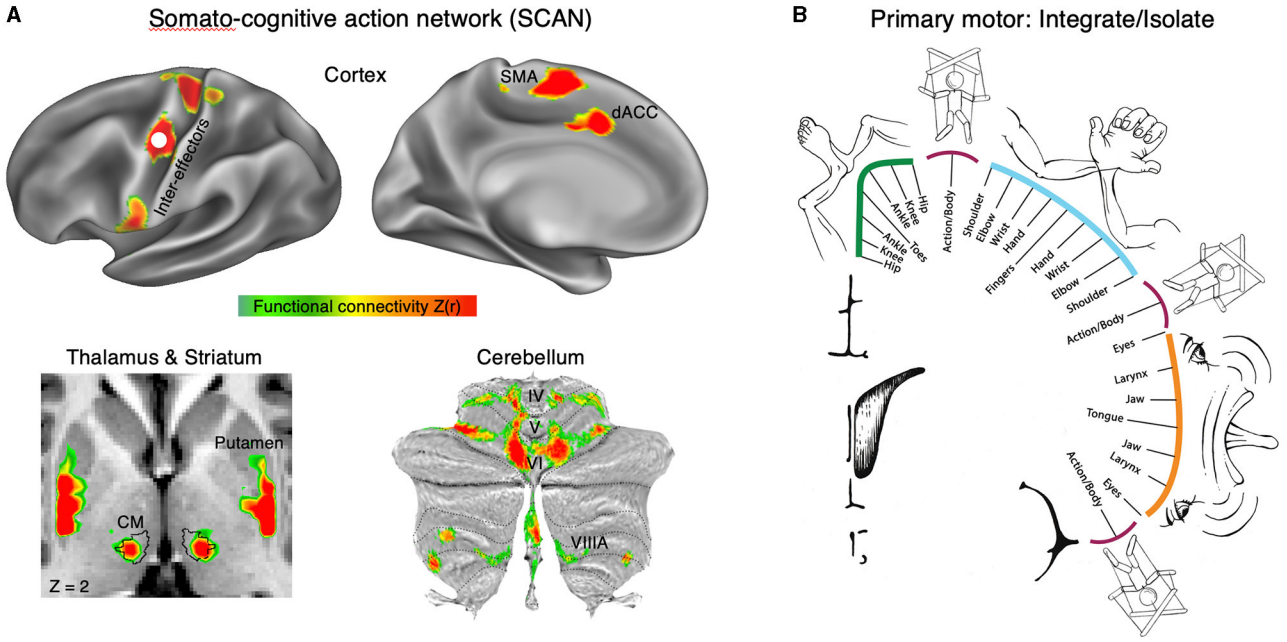

FIGURE 1
Somato-cognitive action network (SCAN). **(A)** Resting state functional connectivity (RSFC) seeded from the middle inter-effector node in primary motor cortex (bilaterally) in a representative individual (P1; 356 min resting-state fMRI). In cortex the SCAN includes three inter-effector nodes (superior, middle, inferior) that alternate with effector-specific foot, hand and mouth primary motor regions, as well as two nodes on the dorsal midline in the SMA (supplementary motor area) and dACC (dorsal anterior cingulate cortex) that are interleaved with the effector-specific regions of the SMA/pre-SMA. In thalamus, the centromedian nucleus [CM; black outline (Ewert et al., 2017)] is part of the SCAN. In the striatum, the dorsal posterior putamen forms part of the SCAN. In the cerebellum, crus VI and para-vermian VIIIA are part of the SCAN. Functional connectivity [Z(r)] in cortex was thresholded from 0.35 to 0.6, and from 0.15 to 0.3 to account for the lower signal-to-noise ratio. **(B)** In the integrate–isolate model of M1 organization, effector-specific—foot (green), hand (cyan) and mouth (orange)—functional zones are represented by concentric rings with proximal body parts surrounding the relatively more isolatable distal ones (toes, fingers and tongue). The SCAN inter-effector regions (maroon) sit at the intersecting points of these fields and support integrative, allostatic whole-body control.

Vagus nerve stimulation to enhance motor learning and myelin repair

Closed-loop VNS was recently approved by the FDA to restore upper limb mobility for patients with stroke. Preclinical and early clinical studies suggest that closed-loop VNS improves recovery from conditions such as spinal cord injury, traumatic brain injury, post-traumatic stress disorder, and addiction. Despite the wide-ranging etiology of these conditions, the therapeutic model is similar; VNS is paired with a relevant rehabilitation protocol. The precise timing of stimulation is a key element to drive specific circuit plasticity and functional recovery. Yet, VNS activates widespread brain networks, raising the question of how closed-loop VNS may lead to circuit-specific alterations in plasticity and functional recovery.

Research from Dr. Cristin Welle's lab has recently found that VNS can enhance motor learning in healthy animals through cholinergic-mediated reinforcement learning (Bowles et al., 2022) (Figure 2). VNS elicits brief cholinergic signaling from the basal forebrain (BF) and brief inhibition of cholinergic neurons during VNS prevents enhanced motor learning. The timing of these signals is critical, as VNS paired with a successful reach improves learning, but VNS paired with the initiation of movement does not. Early results also show evidence that VNS can increase myelination of neural circuits, with specificity of sheath placement increased during VNS paired with success. Together, these results indicate that VNS augments cholinergic reinforcement to enhance learning and plasticity in motor systems.

Cutting edge physiology in pursuit of adaptive DBS

An ongoing exciting development in the field is aDBS, a paradigm that uses brain activity or wearable sensors to deliver stimulation when symptoms are present. By only delivering intermittent stimulation, aDBS may improve therapeutic efficacy, reduce side effects, and prolong DBS device battery life. However, challenges remain in determining the optimal approach to design aDBS algorithms, including which control signal(s) to use, how to determine patient-specific biomarkers, and how to account for changes in brain state (e.g., during sleep and across circadian cycles).

Toward automated, data-driven, adaptive DBS

aDBS has great potential to improve therapeutic efficacy, however significant scalability challenges remain due to

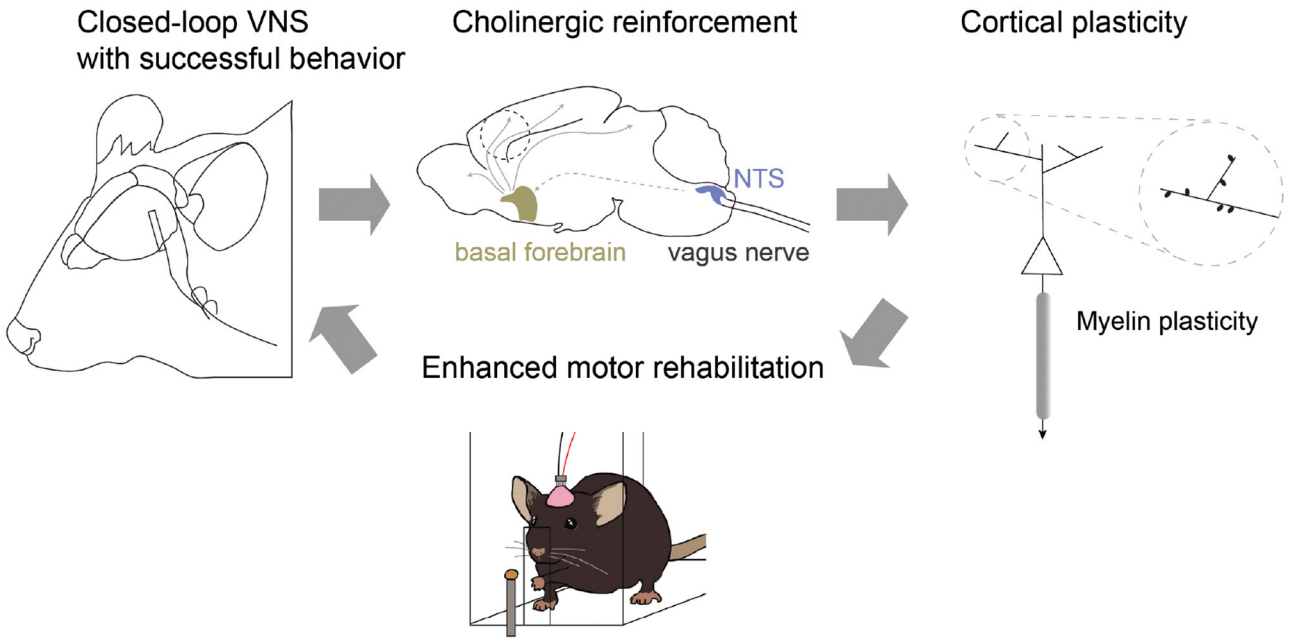

FIGURE 2
Closed-loop vagus nerve stimulation (VNS) for reinforcement learning. VNS paired with successful behavioral outcome drives phasic cholinergic signaling from the basal forebrain and modulates neuronal representation of outcome within motor cortex. In addition, closed-loop VNS influences myelin plasticity and repair within motor cortex, restoring motor function in models of demyelination. Together, these results suggest a model in which closed-loop VNS can enhance behavioral reinforcement cues through cholinergic neuronal activity to promote circuit-specific plasticity and enhanced learning.

complexities of implementation. To this end, Dr. Simon Little's lab introduced three proof-of-principle adaptive algorithms toward personalized, automated programming. First, they demonstrated an automated machine learning pipeline for biomarker selection in three patients with PD. Multiple methods converged to show that cortico-basal finely tuned gamma (FTG) outperformed classical subcortical beta as an optimal biomarker. aDBS parameterized against either subthalamic (STN) or cortical FTG showed a significant increase in ON times and improved quality of life (Oehrn et al., 2023). Second, they introduced a new, fully data-driven algorithm in which all parameters—from biomarker identification to aDBS optimization—were parameterized in an automated manner, fully remotely, in patients' own homes. This demonstrated a reduction in dyskinesia and improved movement speeds in a natural typing task. Finally, they demonstrated multi-night at-home sleep recordings and negative interactions between beta and slow waves, in addition to a fully data-driven aDBS algorithm for sleep stage modification targeting NREM sleep (Anjum et al., 2023; Smyth et al., 2023). Their work shows that personalized nighttime stimulation adjustments were well tolerated with initial evidence that this technique might be able to optimize NREM slow waves linked to disease progression.

Neural biomarkers of mood: implications for the closed-loop debate

DBS of the subcallosal cingulate (SCC) and ventral capsule/ventral striatum (VC/VS) has been used for treatment-resistant depression (TRD) with variable success. Improving our fundamental understanding of the neurophysiological basis of mood state variation would allow for a more data-driven approach to optimizing stimulation delivery, which in turn would likely improve the consistency and predictability of outcomes (Allawala et al., 2021). Dr. Sameer Sheth's lab conducted intracranial recordings in depression-relevant regions in a cohort of three patients with severe depression that were enrolled in an early feasibility trial (NCT03437928) of individualized DBS guided by intracranial recordings (UH3 NS103549). The outcomes of the first subject in the trial were recently reported (Sheth et al., 2022). Each subject was implanted with two pairs of permanent DBS leads for stimulation delivery in the SCC and VC/VS, along with temporary stereo-electroencephalography electrodes for neural recordings. After surgery, subjects underwent inpatient monitoring for 9 days, during which they obtained frequent self-report measures of depression severity and simultaneous network-wide neural recordings. The results indicated that decreased low-frequency and increased high frequency neural activity across prefrontal regions correlated with reduced depression severity. Based on these observations, they built a model to predict depression severity from neural activity and found that high frequency (beta, gamma) power in the dorsal anterior cingulate cortex significantly predicted depression severity across all three subjects. When the model was not constrained to features from a single region, individual-specific sets of spatiospectral features predictive of symptom severity emerged that reflected the heterogeneity of the disorder (Xiao et al., 2023). The ability to predict depression severity based on neural activity increases our understanding of the neural basis of depression and provides a target neural state for personalized stimulation interventions.

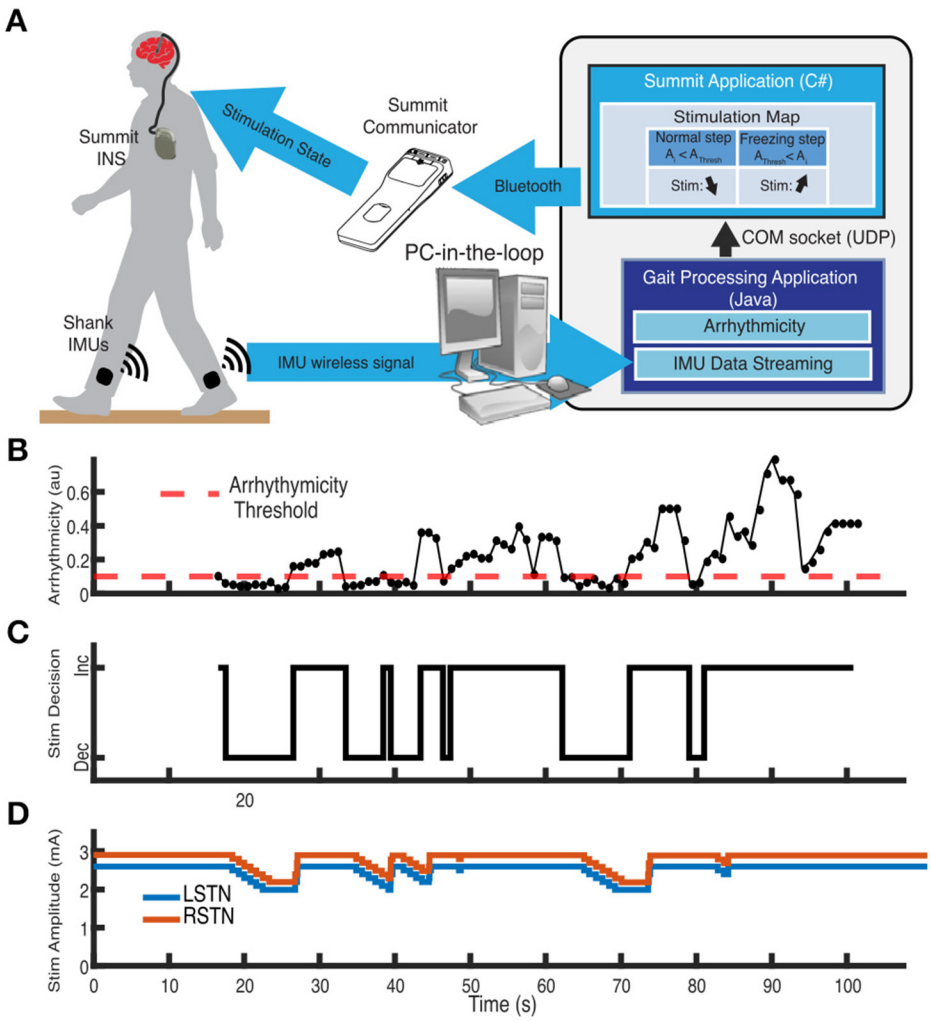

FIGURE 3
Example of adaptive DBS system for freezing of gait in Parkinson's disease using kinematic inputs. **(A)** Schematic of distributed aDBS system. Inertial measurement unit (IMU) data is streamed in real-time to a PC-in-the-loop. Gait arrhythmicity is measured from the IMU data. A decision to increase or decrease stimulation intensity is made depending on whether the measured arrhythmicity is above or below an established threshold, which is then communicated back to the Summit RC+S neurostimulator via the Summit communicator. **(B)** Measurement of the real-time arrhythmicity over the course of a stepping-in-place task relative to the threshold. **(C)** Stimulation decisions to increase or decrease stimulation based on the arrhythmicity. **(D)** Adaption of stimulation amplitude of the two subthalamic nuclei in response to the gait arrhythmicity. Adapted from Melbourne et al. (2023).

Sensing motion: real time kinematic feedforward and feedback inputs for aDBS

Closed-loop or aDBS relies on inputs that are relevant to neurological symptoms. The primary focus to date has been on using relevant neural signals as inputs for aDBS, often from the site of the DBS lead. However, kinematic inputs derived from wearable sensors on the body offer an opportunity for directly measuring a behavior or symptom of interest with high fidelity. There is growing interest in using kinematic data to classify behaviors. Symptoms such as tremor and freezing of gait can be reliably measured using inertial measurement units placed on various parts of the body. These data can then be used to adapt stimulation to provide therapy in a demand-based fashion. Initial studies have demonstrated the successful implementation and tolerability of an aDBS system based on real-time kinematic inputs for both tremor, across both Parkinson's disease and essential tremor, as well as freezing of gait. These approaches offer the advantages of: not requiring sense-friendly stimulation configurations, being resistant to stimulation-related neural artifact, having a much higher fidelity signal in comparison to subcortical neural signals recorded at the site of stimulation, enabling the use of rapid ramp rates to provide changes in therapy, and allowing adaptation of other stimulation parameters (e.g., frequency). Measuring the kinematics of the symptom targeted for therapy at different DBS intensities facilitates the choice of a therapeutic range that aDBS will be constrained to, thus enabling precise, safe, and tolerable aDBS, driven by relevant kinematics (Figure 3).

Advances in commercially available neuromodulation technologies

Collaboration between academia and industry is central to progressing the field of DBS. The DBS Think Tank features an industry blitz each year to highlight novel therapies and discuss

challenges and opportunities in translating new technologies into products for clinical use.

Advances in brain sensing

Technological advances in implantable neural stimulators have made it possible to sense brain signals from DBS leads while delivering stimulation. Sensing technology has created unique insight into patient-specific biomarkers and brain states not only when patients are in the clinic but also in the home setting. Commercially approved devices are now on the market with embedded brain sensing technology making chronic brain data during routine clinical care accessible worldwide (Chen et al., 2019; Elder et al., 2019; Arlotti et al., 2021; Goyal et al., 2021). The Medtronic Percept™ device with BrainSense™ technology has now been implanted in tens of thousands of patients globally including for the approved indications of Parkinson's disease (PD), essential tremor, dystonia, epilepsy, dystonia, and obsessive-compulsive disorder (OCD).

Evidence is building that BrainSense may be used to guide DBS programming setup and optimization in movements disorders and epilepsy (Feldmann et al., 2021; Buijink et al., 2022; Fasano et al., 2022; Strelow et al., 2022; Chua et al., 2023; Swinnen et al., 2023). Recent studies in Parkinson's disease suggest BrainSense can be used to streamline and reduce the time for initial DBS programming (Binder et al., 2023; Lewis et al., 2023), troubleshoot difficult cases, identify medication interactions, and mitigate potential overstimulation (Kern et al., 2022; Vaou et al., 2023). Simplified data visualizations are also being developed to expand access to the insights learned to date (Thompson et al., 2023). Collectively, these case studies demonstrate the value of chronic brain signals as objective feedback for simplifying and tailoring DBS therapy management.

Additional research is exploring how BrainSense can be used for aDBS in PD, where an investigational Percept software unlock allows automated stimulation amplitude modulation. The Medtronic-sponsored ADAPT PD trial is evaluating the safety and effectiveness of aDBS (Herrington et al., 2023), whereas several feasibility studies are reporting potential benefits of aDBS over continuous DBS (Nakajima et al., 2021; Oehrn et al., 2023; Smyth et al., 2023). Furthermore, primarily through the NIH BRAIN Initiative other investigations are focusing on developing BrainSense biomarkers and classifiers of neuropsychiatric disorders including treatment-resistant depression, OCD and Tourette syndrome (Vissani et al., 2022; Alagapan et al., 2023; Butson et al., 2023).

In general, as DBS technology continues to advance it will be critical for product designers to consider the balance between routine but clinically meaningful innovation and foundational research. Therefore, Percept is an example platform that has been intentionally designed to be software and firmware upgradable for unlocking both ease of use features as well as advance technical capabilities.

Toward automated image- and outcomes-guided DBS

Boston Scientific Neuromodulation (BSN) focuses on developing powerful, clinically impactful technology to enable precision control of novel stimulation patterns in the time domain, and automation of stimulation targeting, using image- and outcomes-guided programming strategies.

The Chronos research software unlocks pulse-by-pulse stimulation composition in chronically implanted patients allowing researchers to explore novel stimulation patterns with the goal of improving therapy for current and future indications and expanding understanding of DBS.

Image-guided programming tools GUIDE XT and STIMVIEW XT, provided through a collaboration with Brainlab Inc., allow clinicians to visualize the lead and the stimulation within the patient's own anatomy during surgical planning and patient programming. By correlating anatomy and outcomes from individual stimulation locations across multiple subjects, BSN, in collaboration with multiple centers, is generating probabilistic maps to define "hot" and "sour" spots for stimulation. DBS Illumina 3D then allows clinicians to specify predefined target and avoidance regions and instantly recommends a set of stimulation parameters. BSN is working to make this algorithm commercially available in the future.

Outcomes-guided programming tools, such as Clover, allow the clinicians to further refine initial programming solutions. Clover assists clinicians programming linear (Sasaki et al., 2021) or directional (Wenzel et al., 2021) leads while evaluating multiple symptoms (Gülke et al., 2022). The algorithm is incorporated in the StimSearch™ software and uses physician provided symptom and side effect scores to generate suggested stimulation settings to explore the search space. StimSearch™ interfaces with the BSN clinician programmer and can be made available upon request.

Advances in digital health integration

Advances in hardware platforms, mobile computing, and sensor technology (with features like bluetooth low energy and upgradable software), along with a favorable regulatory and reimbursement landscape, have resulted in greater digital health integration with device-aided therapies like neuromodulation. Abbott presented a digital health vision for this field by introducing the Neurosphere™ Virtual Clinic, a telehealth platform that helps connect patients with their clinicians so their therapy can be evaluated and adjusted remotely. Digital health integration may expand access, improve outcomes, and drive efficiencies to better serve patients. These technologies may be crucial as DBS expands to other indications, for example, treatment resistant depression, where issues like access, compliance with therapy, and follow-up care are critical because the patient population may be vulnerable. Leveraging ubiquitous consumer-grade technology enables DBS devices to provide tailored solutions through already familiar interfaces and fit better into patient lives.

Updates in neuromodulation for epilepsy

NeuroPace has ongoing clinical trials studying neuromodulation in epilepsy. The NAUTILUS Study (NCT05147571) is a pivotal study to determine if the RNS System is safe and effective as an adjunctive therapy for the treatment of primary generalized seizures in individuals 12 years and older who have drug-resistant idiopathic generalized epilepsy (IGE). This prospective, multicenter, single-blind, randomized, sham stimulation controlled study will enroll up to 100 participants within the United States. Leads are placed bilaterally in the centromedian nuclei. Primary outcome measures are the 12-week post-operative serious device-related adverse event rate and the time to second generalized tonic-clonic seizure.

The RNS System Lennox-Gastaut Syndrome (LGS) Feasibility Study (NCT05339126) is an NINDS funded Brain Initiative study intended to generate preliminary safety and effectiveness data for brain-responsive neurostimulation of thalamocortical networks as an adjunctive therapy in reducing the frequency of generalized seizures in patients 12 years or older with LGS who are refractory to antiseizure medications. The study is ongoing and up to 20 subjects will be implanted. Leads are placed bilaterally in the prefrontal cortex and centromedian nuclei.

The Patient nSight Report has been updated with expanded patient-specific content to help physicians more efficiently review patient data prior to clinic visits.

An updated version of the Patient Data Management System interface has been released that includes *Simple Set*. This expanded feature allows a complete patient-specific programming set to be selected and sent to the RNS Tablet to streamline physicians' in-clinic experience.

Passive monitoring to guide Parkinson's disease treatment

Evaluating DBS motor outcomes for Parkinson's disease is challenging due to treatment and patient heterogeneity. While clinical scales such as the Movement Disorders Society (MDS) Unified Parkinson's Disease Rating Scale (UPDRS)-III are the gold standard, they provide intermittent, subjective snapshots during clinical visits. In contrast, passive monitoring of patient symptoms offers continuous, objective monitoring of motor fluctuations in Parkinson's disease in real-life scenarios (Evers et al., 2019; Omberg et al., 2022; Klein and Bloem, 2023). Rune Labs assessed the utility of passive wearable monitoring combined with population level monitoring in (1) predicting short-term DBS effectiveness, and (2) characterizing long-term symptom trajectories. Using shorter time scales (days) they built a model to predict DBS effectiveness in suppressing tremor. Local field potential (LFP) fluctuations and sensor locations were the most important features identified. This model could provide the basis for sensing-guided programming targeted to specific symptom reduction. Over longer time scales, assessing DBS effects becomes challenging due to medication and stimulation changes; they focused on gait metrics less influenced by levodopa or DBS, associated with cholinergic system deficits (Figure 4). They show that such markers may be ideal in capturing progressive progression of Parkinson's disease.

AlphaDBS for closed-loop DBS

The AlphaDBS System is a local field potential (LFP) sensing enabled, CE-certified, fully implantable, DBS system for the treatment of Parkinson's disease. The system records LFP power in a patient-specific selected band continuously, and this sensing data is provided to the clinician via a cloud-based data management system. The system can operate in both a conventional and aDBS (cDBS-aDBS) mode. In aDBS LFP beta power is used as the input variable to the adaptive proportional control algorithm that computes a new stimulation amplitude every minute (Arlotti et al., 2021).

To date, 11 patients requiring a DBS implantable pulse generator exchange and five new patients have been implanted in a European feasibility study comparing aDBS vs cDBS (ClinicalTrials.gov ID NCT04681534). When, at the end of the study period, patients were asked to blindly choose between the two stimulation modes received, 90% of them preferred aDBS over cDBS.

Data available so far in the cloud-based data management system consist of more than 40,000 h of LFP recordings, with two patients receiving aDBS for more than 1 year and 3 for more than 6 months after the end of the study period. Preliminary analyses show the ability of recorded LFPs to track daily activities, particularly sleep, and to monitor motor behaviors.

Advances in Europe

Effect of high frequency STN DBS: beyond beta suppression and the potential implications

Continuous high frequency subthalamic DBS is an effective therapy for advanced Parkinson's disease, which raises the questions of: (1) whether aDBS, which requires simultaneous sensing and stimulation, is necessary, and (2) whether the consideration for efficacy and complexity balance still justifies the research on aDBS for PD. Continuous high frequency STN DBS induces changes in the network beyond the suppression of pathological synchrony in the beta frequency band. It functionally disconnects STN from the basal ganglia network.

Research from Dr. Huiling Tan's lab has shown that continuous high frequency STN DBS can reduce activities over a broad frequency band including alpha and gamma oscillations (Wiest et al., 2023b). Recent studies have also reported the high frequency resonant neural activity (ERNA) in the STN and the GPi (Sinclair et al., 2019; Johnson et al., 2023; Wiest et al., 2023a), and the amplitude and frequency of the ERNA change with time after the stimulation is switched on, reflecting synaptic depletion. These changes are not specific to Parkinson's disease, but also observed in cervical dystonia (Wiest et al., 2023b).

Continuous high frequency STN DBS over-suppresses gamma oscillations during voluntary movements, which helps invigorate

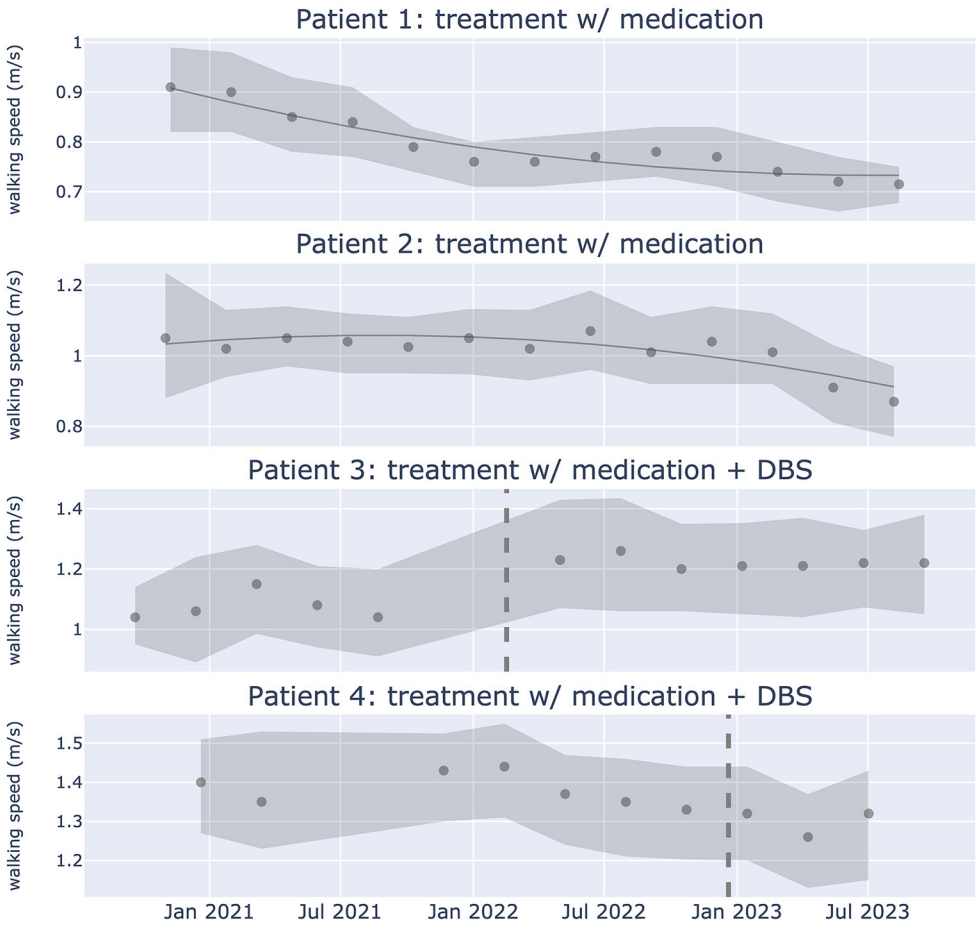

FIGURE 4
Differences in long term walking speed trends with and without DBS treatment. Gait dysfunction in PD is associated with the cholinergic system, and may be a more sensitive biomarker than other motor signs of PD that respond to medication or DBS. Plots show walking speed over a period of 2.5 years from 4 patients. Walking speed (meters/second) was captured using iPhone actigraphy during real world activities. Scatter points represent median walking speed during a 3 month window, shaded error bars represent the 25th and 75th percentile of walking speed respectively. Dotted line represents the date in which DBS was implanted. Data from 32,550 walking events, across 321.17 walking hours.

the movements, compared to beta-triggered aDBS. Therefore, even though beta-triggered aDBS led to less stimulation during reaching movements, it improves the movement performance to the same level as continuous DBS (He et al., 2023). Meanwhile, the ERNA reduced in frequency and amplitude with time during cDBS indicating synaptic depletion, whereas ERNA remained high during aDBS due to the bursting nature of the DBS, indicating a different synaptic status (Wiest et al., 2023a).

The mechanism of continuous DBS also has an impact on sleep. Evidence has started to converge that beta bursts in STN LFPs persist during NREM sleep in human patients, although the occurrence is less frequent. Increased beta and low gamma during NREM correlated with arousal and sleep fragmentation index, which will be reduced by cDBS. However, cDBS may interrupt other physiologically important activities during sleep such as the sleep spindles, slow waves, and their temporal relationship. aDBS has the potential to suppress the pathological signals underlying sleep fragmentation, and at the same time preserve or increase those activities that are functionally important to recover normal sleep structure.

Do the parkinsonian basal ganglia dream of beta oscillations?

Sleep has robust effects on discharge rate and pattern of neurons in the basal ganglia of naïve (normal, control) non-human primates (NHPs). NHPs treated with MPTP exhibit massive degeneration of midbrain dopaminergic neurons, depletion of striatal dopamine, as well as severe sleep fragmentation. Synchronous beta oscillations persist during rapid eye movement (REM) and non-REM (NREM) sleep and entrain the cortical EEG. LFP beta oscillations recorded from the basal ganglia of Parkinson's patients exhibit a robust circadian rhythm; however, even during NREM sleep the level of beta oscillations is higher than in the control (dystonia).

DBS techniques are improving. Classical DBS therapy is given continuously (24/7), probably inactivating the basal ganglia (by high-frequency depletion of afferent and efferent synaptic vesicles) and allowing compensation by the cortical networks. Current sensing devices can enable closed-loop DBS therapy that inactivate the basal ganglia only when they "misbehave" (i.e., during long episodes of beta oscillations). Future closed-loop DBS therapy would use phase, frequency, and circadian information to suppress beta oscillations and to augment sleep delta oscillations. This would restore normal sleep architecture and remove accumulated misfolded proteins and may slow down the progression of REM sleep behavior disorder and Parkinson's disease.

Going on with DBS and gait

Parkinsonian gait disorder and freezing of gait (FoG) remain therapeutic challenges. Besides current troubleshooting options for STN DBS (Pötter-Nerger and Volkmann, 2013), further approaches should be based on hypotheses of gait pathophysiology. Recent intraoperative observations from microelectrode recordings of basal ganglia single neurons during a stepping task in PD revealed a nucleus specific modulation of single unit activity with nigral neurons (SN) modulated during attentional, cognitive cues (Gulberti et al., 2023), supporting the therapeutical approach of STN-SN co-stimulation. In line with these findings, combined STN+SN-DBS improved gait quality in postoperative patients particularly during gait conditions with increased attentional load (Horn et al., 2022). Another hypothesis proposes FoG to be a phenomenon of chronic "overstimulation" by DBS. One potential option would be a down-regulated, fiber-specific "short-pulse" stimulation, which was shown to equally improve objective gait parameters as conventional DBS in the short-term, but subjectively preferred in about 40% of freezing PD patients (Seger et al., 2021). Future hopes include potential DBS algorithms that drive beneficial neuronal plasticity (Horn et al., 2020) to normalize basal ganglia circuit activity and prevent or delay FoG onset in later stages of the disease. So far, the complex context of the parkinsonian gait disorder and methodological restraints limit the interpretation of DBS efficacy on gait.

Advances in Asia

Intracranial physiological biomarkers of neuropsychiatric symptoms

STN DBS can be associated with hypomania in both PD and OCD patients, particularly linked to ventral associative-limbic contacts. In the first set of studies, Dr. Valerie Voon's lab deconstructed hypomania operationalized into testable cognitive constructs. Using an emotional processing task, acute STN stimulation in PD patients at 10 Hz shifted to a positive subjective emotional bias (Mandali et al., 2020) and increased alpha power (Muhammad et al., 2023). This shift occurred with both acute (Mandali et al., 2020) and subacute stimulation with ventral contacts (Wang et al., 2023) (Figure 5). Second, high frequency acute STN stimulation of ventral contacts enhanced risk seeking in PD patients. Normative Lead-DBS and Biobank analyses dissociated risk-taking as a function of pre-supplementary motor area (SMA) and SMA anatomical and functional connectivity with STN. Thus, they highlight cognitive dimensions associated with ventral STN stimulation, representing key hypomania symptoms of euphoria and risk-seeking symptoms. In the final study, they highlight resting state theta activity in the bed nucleus of the stria terminalis, and prefrontal theta along with functional connectivity as a resting state biomarker predicting depression therapeutic improvement at 3 months in depressed patients.

Dual target stimulation for treatment-refractory depression

DBS has emerged as a promising therapeutic approach for the treatment of patients with treatment-resistant depression (TRD). However, the underlying mechanisms through which DBS exerts its therapeutic effects are not yet fully elucidated. Previous studies have provided robust evidence indicating the crucial involvement of the bed nucleus of the stria terminalis (BNST) and the nucleus accumbens (NAc) neural circuitry in the processing of negative emotions. In this study, Dr. Bomin Sun and colleagues analyzed local field potentials (LFP) and explored functional connectivity in the circuit involving the BNST and the NAc to assess the mechanisms underlying the therapeutic effect of DBS.

This study recruited a total of 18 patients diagnosed with TRD. Synchronous implantation of intracranial DBS electrodes was performed in the BNST and NAc. LFPs were recorded using the implanted electrodes. Post-surgically, the participants' baseline symptoms were assessed, and LFP recordings were conducted. Following a 6-week duration of DBS treatment, reassessment and recording was performed. The patients were categorized into two groups based on the criterion of achieving a >50% improvement in the clinical scales. Differences in the LFP characteristics and functional connectivity of the BNST-NAc circuit were explored before and after DBS treatment, and between the two groups.

After 6 weeks of DBS treatment, the majority of subjects (13/18) showed significant improvements in depressive symptoms (>50% on Hamilton depression scale, which defined as response group). Compared to non-response group, response group showed significantly modulated oscillatory activities of gamma in BNST and theta in NAc, which had strong correlations with TRD symptoms. Also, the enhancement of unidirectional functional connectivity of the BNST-NAc circuit was exclusively observed, measured by Granger causality. Phase-amplitude coupling in the circuit also supported this functional connectivity, and its strength was also correlated with TRD symptoms. Finally, they found that BNST-NAc functional connectivity enhancement is specific to low-complexity time windows, which may be related to the modulatory effects of DBS.

Therapeutic DBS not only modulated the LFP activities at stimulation site, but also promoted the functional connectivity within the neural circuitry extending from discrete nuclei to complex neuronal networks. This suggests that local stimulation may affect downstream subcortical structures by modulating the

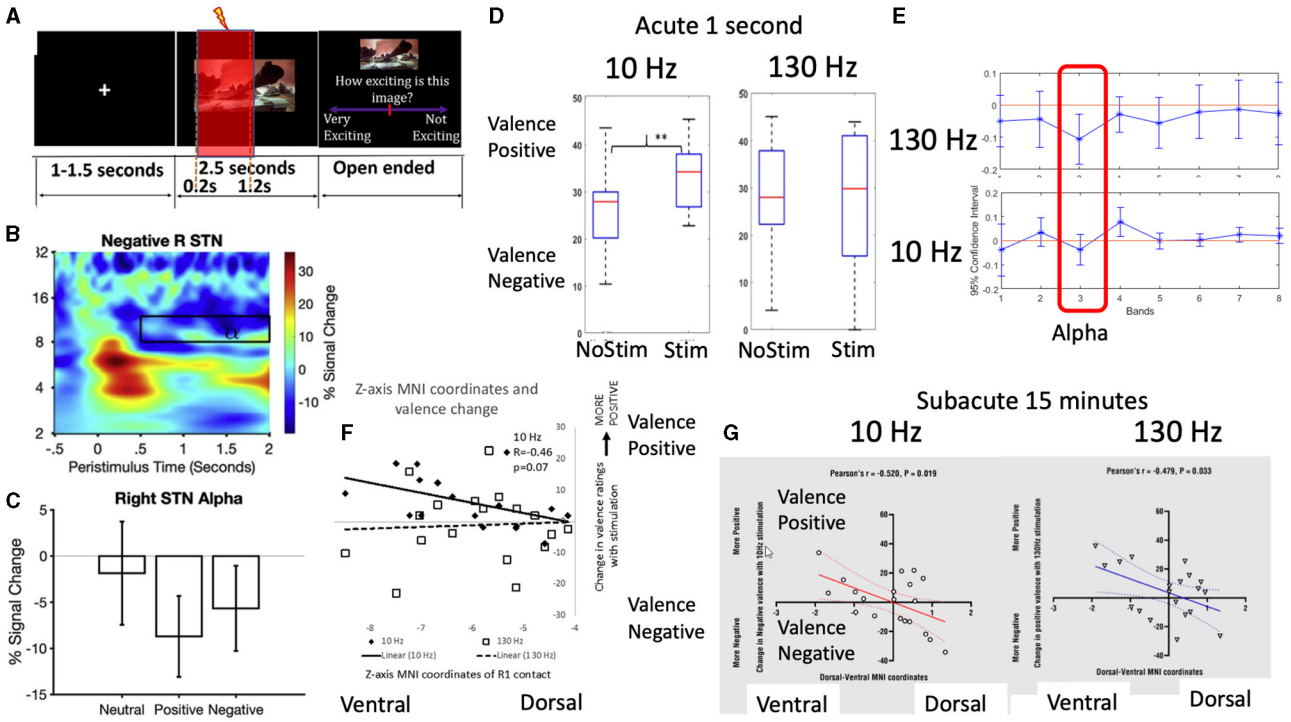

FIGURE 5
Subthalamic stimulation effects on emotional processing and alpha frequency. Intracranial subthalamic physiology recordings were paired with **(A)** a task-based emotional processing task with negative, positive and neutral images and recorded subjective valence and arousal (here shown with 1 second stimulation) (1). The results demonstrated the **(B, C)** expected late alpha desynchronization with affective imagery (1) which has been previously correlated with subjective valence and depression scores. **(D)** Using acute 1 second stimulation, there was a shift toward positive subjective valence bias to 10 Hz (alpha) stimulation but not 130 Hz (clinical) stimulation frequency (1) with **(E)** 10 Hz stimulation increasing alpha synchronization (i.e., loss of alpha desynchronization) (2). Both **(F)** acute 1 second 10 Hz stimulation and **(G)** subacute 15 min 10 Hz and 130 Hz stimulation of ventral contacts (3) was associated with greater positive emotional valence bias.

output pattern of neuronal projections. The modulation of DBS-induced functional connectivity was specific to a transient time window of low complexity, suggesting that one of the ways in which DBS exerts its therapeutic effects may be to entrain disordered neuron populations, reducing background noise and integrating the BNST-NAc circuit.

A variety of clinical responses to thalamic DBS in individual Tourette syndrome patients

The clinical responses to deep brain stimulation (DBS) for severe Tourette syndrome (TS) reportedly vary among patients. Possible solutions to achieve standardized outcomes may be precisely placing DBS electrodes in the "sweet spot" and selecting optimal stimulation parameters. Recent papers have addressed the position of a potential sweet spot and the importance of the neuroanatomy-based approach to DBS programming based on the microlesion effect of the centromedian (CM) thalamic DBS (Morishita et al., 2022) and connectomic analyses (Morishita et al., 2021) respectively (Figure 6). These reports have indicated that the dorsal border of anteromedial CM and ventrolateral thalamic nucleus may be a sweet spot. Another issue to be considered for successful TS is stimulation-induced neuroplasticity, as recent papers addressed that CM thalamic DBS may result in either beneficial or ominous effects in the long term (Smeets et al., 2017; Kimura et al., 2019). To induce beneficial neuroplasticity, selecting the optimal stimulation parameters is critical based on careful observations of the clinical symptoms. To evaluate the effects of CM thalamic DBS, computational measures as proposed for obsessive-compulsive disorder (Sakai et al., 2022) may be applied for TS, and this kind of computational modeling of behavior may be helpful to guide the optimal clinical course of TS patients who receive DBS therapy.

Neuroethics cases: dilemmas that inform the future of neuromodulation

Life after a beneficial experimental DBS trial: new opportunities and challenges

In the U.S. and other countries, patients with severe treatment-resistant conditions (e.g., refractory depression, OCD) whose symptoms improve with an implantable neural device during a clinical trial, may not be able to keep the device functioning after the trial ends (Underwood, 2017; Lázaro-Muñoz et al., 2018, 2022; Drew, 2020, 2022). There are several potential factors that can

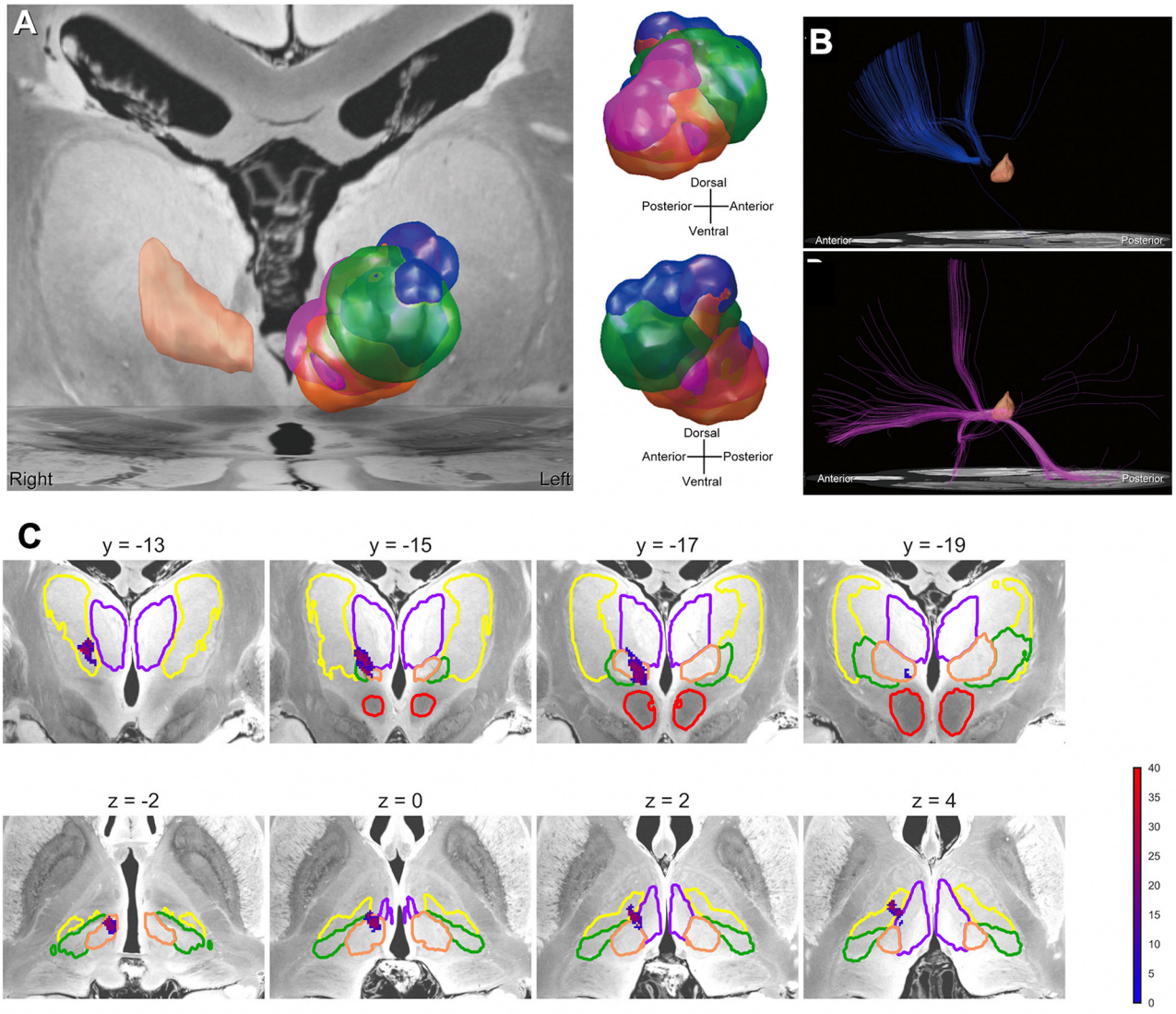

FIGURE 6
Mapping the effects of DBS for Tourette syndrome. **(A)** VTAs related to therapeutic stimulation and side effects. Each VTA color represents areas associated with the following effects: blue = therapeutic effect, orange = dizziness, green = paresthesia, and purple = depressed mood. The peach-colored region in the right hemisphere is the CM nucleus. **(B)** Normative connectome from VTAs related to therapeutic stimulation and side effects. The normative connectome from VTAs related to the therapeutic stimulation (above), and depressed mood (below). The peach-colored region is the CM nucleus. **(C)** Precision mapping of implanted deep brain stimulation electrodes in an atlas associated with tic improvements in the thalamus. The color bar represents the percentage improvement in tic symptoms.

contribute to losing access to a device, including the Institutional Review Boards not requiring a plan for post-trial care for the study to be approved, funding bodies may not be willing or able to assist, or the research teams who conduct the trials may not be able to negotiate post-trial access with the device manufacturers (Figure 7).

In the U.S., even if a participant's treatment-resistant conditions improve with the experimental device, health insurance providers may deny coverage for post-trial device maintenance on the basis that the device is being used for an experimental indication in the trial and determine it is not "medically necessary" (Lázaro-Muñoz et al., 2018). This would shift the financial burden to participants, which can be prohibitively expensive for many individuals. Finally, even if the participants can finance the costs of post-trial care, device manufacturers may go out of business, cease production of the device or some necessary component of the device, or stop servicing the necessary software, leaving patients without access (Strickland and Harris, 2022). This can create unease among former trial participants and lead to deprivation harms, as a DBS trial participant stated: "*It would be kind of cruel to give a guy this much life back and snatch it away just because of a few pennies, although it's more than a few pennies*" (Lázaro-Muñoz et al., 2022; Hendriks et al., 2023). Implantable device deprivation harms (IDDH) risk exposing patients to severe rebound effects if the device stops functioning (Vora et al., 2012) and could lead to further morbidity or even mortality (e.g., DBS for TRD and increased risk for suicide).

Dr. Gabriel Lázaro-Muñoz and colleagues are calling for stakeholders, including funders, device developers, institutional review boards, hospitals/researchers, to develop adequate post-trial *maintenance* plans (PTMP) to ensure access to the necessary hardware, software, and maintenance for a period of time after the

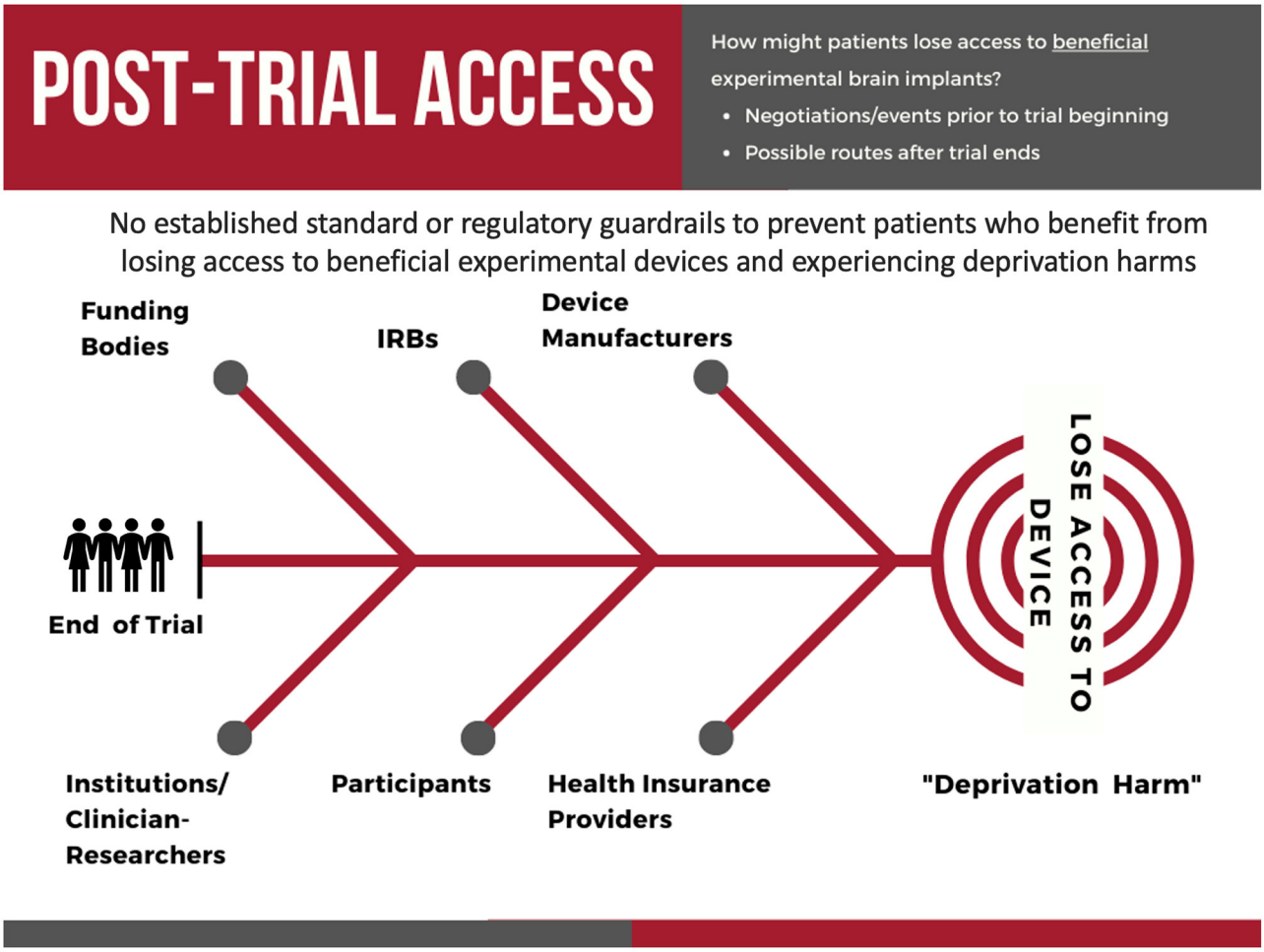

FIGURE 7
The key stakeholders involved in and potential pathways by which participants in experimental neural device trials may lose access to their neural implant after the conclusion of a clinical trial.

trial ends (e.g., 5 years of maintenance from the time the trial ends). This will allow participants further time to strengthen their case that health insurance providers should cover some costs, allow time for the device to be approved by the FDA, or allow the participant time to look for other alternatives. What we cannot allow as a society is to have people with severe treatment-resistant conditions, who have contributed to our scientific and medical understanding of the brain by allowing us to use their brains to test these devices, go back to life with a severe treatment-resistant condition when we have the technology to manage their condition already implanted in their bodies.

Neurotech justice at the bedside: thinking about what we say to patients about technology

Neuromodulation has a reputation problem. Referrers and patients alike view neurosurgical interventions as risky and often do not associate neurosurgical treatment with improved function or quality of life (Mitchell et al., 2023). Indeed, a recent study showed that of the 2,487,819 patients in the National Inpatient Sample with movement disorders between 2012 and 2019, only 29,820 had a procedure involving neuromodulation. This number was markedly less for patients of color as well as rural patients, indicating a disparity in access to care. This access disparity likely represents a multifactorial problem from sociodemographic barriers, to care to patient and provider perceptions of surgery, to provider and systemic biases. Dr. Theresa Williamson's studies have shown that Black and Hispanic patients for example report worse quality of life outcomes and pain and physical dysfunction while also being less likely to undergo surgical treatment [(Williamson, 2023) and in press]. One proposed mechanism for bias and potential for improvement in neuromodulation equity is to improve a patient's understanding of surgical benefit and risk and trust in a provider by tailoring our communication with patients who have surgical pathology. Their studies show that all patients and patients of color find shared decision-making pamphlets and conversations to be easy to use, important, and meaningful. Figure 8 illustrates key to communication to improve goal-concordant care.

Figure out	Figure out what a patient is bringing to the table.
Ask and listen	Truly ask and listen.
Offer	Offer facts. Patients love facts.
Give	Give numbers but don't hide behind them.
Understand	Understand that patient understanding and expectation is associated with outcome.

FIGURE 8
Framework for bidirectional, surgeon and patient communication.

Keeping the human in the loop: considerations regarding trust, responsibility, and justice

Large investments to address the failure of, or provide an alternative to, pharmacotherapy and other interventional strategies for neurologic disease and major mental health disorders have led to significant advances in DBS, including the introduction of rechargeable systems, directional electrodes, and adaptive systems. However, as we develop and use these advances it is key to *keep the human in the loop*. People's attitudes and beliefs about these technologies are key to their acceptance and uptake, and addressing structural and attitudinal barriers is key to improve their availability and accessibility. Dr. Laura Cabrera provided three considerations as we think on the importance of keeping the human in the loop. The first relates to social justice considerations. No matter how good the technology developed is, it is problematic if people that need it cannot get it; this includes issues of geographic availability of centers offering these technologies to lack of physicians willing to refer and continue caring for patients implanted. A second practical consideration relates to trust – not only trust toward the medical system, but also the patient's trust toward their devices. Finally, the use of these types of devices might put into question views about who or what is responsible for outcomes.

Artificial intelligence in neuromodulation

Clinical decision support systems for DBS

The field of clinical DBS is currently benefiting from amazing new technological developments in both the hardware and software tools associated with commercial DBS systems. However, the financial investments and industrial decisions that enabled those new clinical technologies were made 10+ years ago, during a time of lofty expectations for clinical and commercial growth in DBS. Unfortunately, those predictions have proven inaccurate, with anemic growth over last few years. The exact root of this issue is certainly multifactorial. Nonetheless, it is clear that something needs to change to reignite clinical growth if we are to justify the continuation of large R&D budget allocations to DBS. One hypothesis is that the field of clinical DBS has reached a bandwidth ceiling for working within a tertiary care center model. As such, an opportunity to facilitate growth may be in democratizing the management and analysis of DBS patients to a wider spectrum of neurologists via algorithmic tools. In turn, academic and industrial research teams have been working to develop prototype systems for many years, and the first wave of FDA-approved AI-based DBS clinical decision support systems are becoming available.

If Netflix did neuromodulation: a framework for behaviorally driven, scalable programming

Assessment of the human motor system is a core component of evaluating and monitoring neurological diseases. However, today it is typically confined to the clinic. Machine Medicine collected a large dataset of high-quality, clinician-labeled clinical videos of MDS UPDRS-III motor assessments. Applying machine learning and software engineering across the stack (i.e., mobile, web, DevOps, and algorithm training and design), they developed and launched a fully automated pipeline, including administration of an abbreviated motor assessment, activity recognition, and disease severity estimation (Figure 9). Data capture requires the patient's engagement and their smartphone or tablet; otherwise, the pipeline requires no input from a clinician or other human agent, meaning it is highly scalable. This tool could be applied to data-intensive problems such

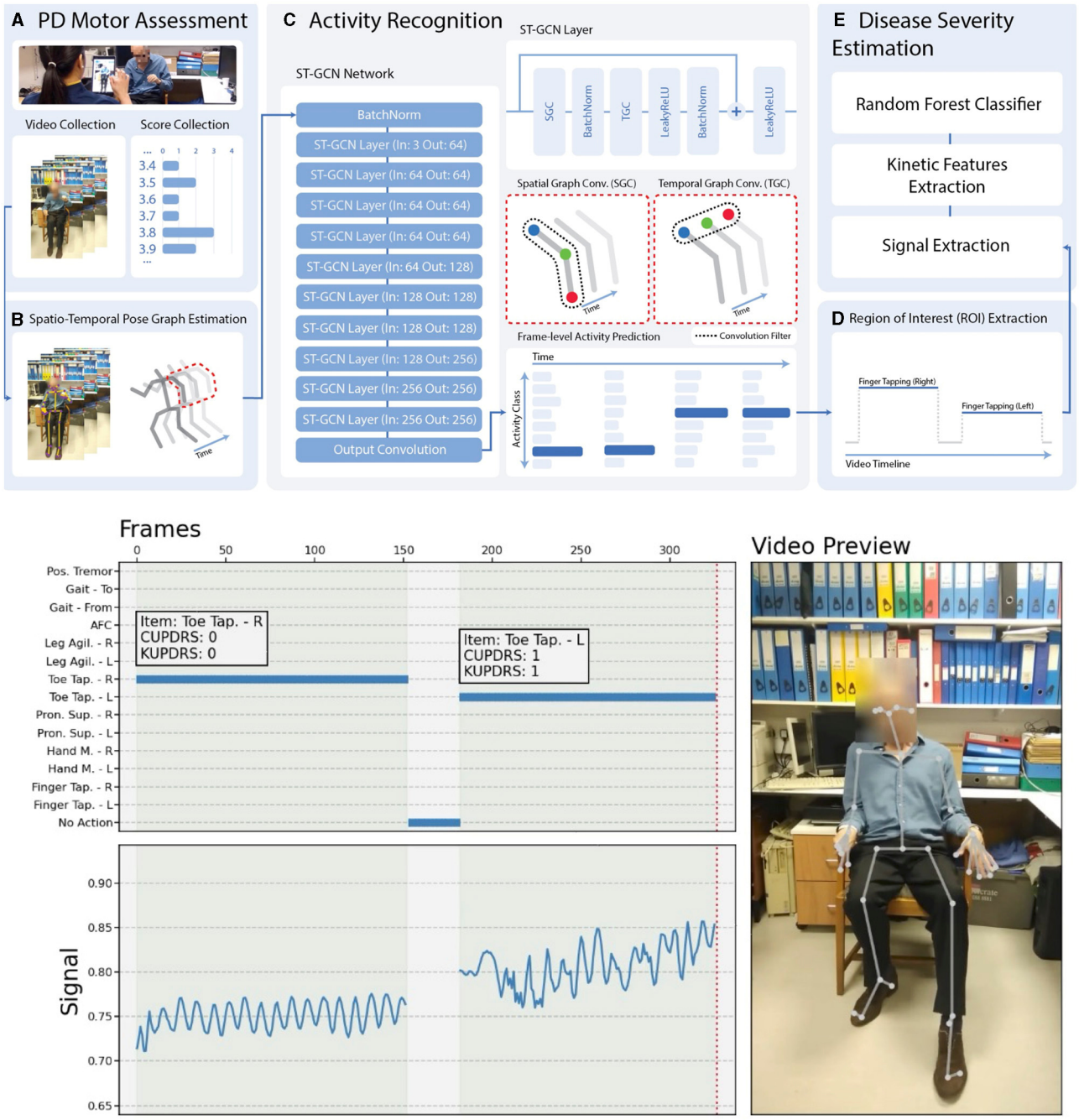

FIGURE 9
Fully automated, video-based motor assessment in Parkinson's disease. Upper half: **(A–E)** Stages of processing a patient video passes through to arrive at a disease severity rating. Lower half: The right panel shows an example video once processed. The upper left panel shows the output of activity recognition (*right toe-tapping*, followed by *left toe-tapping*, with *no activity* indicated in intervening periods). The white boxes show the clinical label (CUPDRS) and the model output (KUPDRS). The lower left panel shows the clinical signal extracted during a relevant activity (in this case, toe-tapping), the features of which are passed to a model for inference.

as programming numerous neuromodulation devices without significantly burdening the clinician, while also delivering an uncomplicated patient experience.

Finally, the technical components required for such a scalable patient-centric system exist in the ecosystem today and, if combined correctly, could employ approaches pioneered by entities such as Amazon and Netflix in their recommender engines to solve conceptually similar and computationally comparable problems at scale.

Empowering precision medicine: AI-driven medical imaging for personalized clinical applications

AI has revolutionized medical imaging, particularly in the context of DBS procedures. In recent years, there has been an exponential growth in studies using AI for medical imaging across three main categories: (1) Image analysis and segmentation, (2) image reconstruction, and more recently, (3) artifact correction and denoising methods. These capabilities are driven by several factors, including the maturation of deep learning algorithms, increased localized computing power, accessible labeled datasets, and the growing awareness of the potential benefits of deep learning in medical imaging.

Focusing on DBS surgery, the impact of AI is profound. A fully automated segmentation process offers several clear advantages, including accuracy (unbiased) and speed (seconds) of inference. It enables improved target localization precision by accounting for patient-specific anatomical differences and reducing electrode placement variability, thereby leading to better outcomes.

AI's impact on medical imaging extends to expanded access to care. AI technology could alleviate the scarcity of specialized neurosurgeons by enabling less experienced practitioners to perform DBS procedures. It also enables tailoring of treatment plans to individual patients.

Although significant advances have been made, there are still challenges to overcome in achieving optimal accuracy and precision. These challenges are related to the quality and diversity of training data, which can vary in terms of imaging protocols, data quality, and anatomical differences. Overall, AI's transformative potential in medical imaging for DBS surgery promises enhanced accuracy, safety, accessibility, and efficiency.

Time scale to measure signatures of mood abnormalities

Treatment-resistant depression (TRD) is a complex neuropsychiatric syndrome that is highly heterogeneous across individuals, and symptoms often fluctuate over many time scales. Increasing evidence suggests DBS can be effective to treat select cases of TRD, but the time scale at which symptoms and biomarkers of TRD should be measured when evaluating the effects of DBS is not well established. Two experts in DBS for TRD provided their rationale and supporting evidence for different time scales.

Days to weeks is both adequate and doable with SCC DBS

Continuous high frequency subcallosal cingulate (SCC) stimulation is one of various strategies for delivering DBS therapy for treatment-resistant depression (TRD) (Mayberg et al., 2005; Holtzheimer et al., 2012). Sustained antidepressant effects can be maintained over many years with SCC DBS using standardized stimulation parameters and minimum current adjustments (Kennedy et al., 2011; Crowell et al., 2019). Leveraging this clinical experience, a standardized method for lead implantation has been developed and validated using patient-specific tractography (Riva-Posse et al., 2014) and reliably executed with consistent outcomes across two centers and four cohorts (Mayberg et al., 2023). However, it remains difficult even for clinical experts to discriminate nonspecific or transient mood symptoms from persistent symptoms that might benefit from dose adjustments. Even when adjustments are made, it takes several weeks to see meaningful clinical effects. Therefore, brain biomarkers that could indicate when a stable response has been achieved and that could also inform when an adjustment is required would have obvious clinical utility. The availability of prototype sensing systems (Medtronic, ACTIVA PC+S; SUMMIT RC+S), embedded in conventional DBS devices, provided a new platform to develop such a readout as part of established clinical protocols (Alagapan et al., 2023). With a focus on past observations of stereotypic acute effects (Choi et al., 2015; Sendi et al., 2021) and the predictable evolution of antidepressant effects over weeks to months across patients, LFP patterns from the SCC were first interrogated to define a common biomarker of the desired outcome—a stable antidepressant response. A neural net classifier was first used to differentiate LFP spectral features corresponding to the beginning and end of six-months of DBS therapy. Next, a novel tool, generative causal explainer (GCE), was used to identify discriminative factors that explained the classifier performance. A separate classifier could be similarly used to differentiate facial features extracted from videos of clinical interviews at the same time points. Coming full circle, the variance in patient response trajectories was correlated with the degree of white matter damage to the DBS target networked defined using DTI; patients with more severe abnormalities did not require a separate classifier, but rather just more time to achieve stable recovery (Alagapan et al., 2023). These first findings appear to replicate in a new cohort of patients (Mayberg et al., 2023). While a control policy has not yet been implemented, these findings support the argument that days to weeks is both an adequate and clinically meaningful time scale to measure and treat a neural signature of major depression across individuals.

Acute effects of patient-specific biomarkers to guide DBS

Dr. Andrew Krystal and colleagues are in the process of carrying out a study of intracranial closed-loop DBS. In this study, stimulus location and parameters are optimized for each patient during a 10-day inpatient stimulus-response mapping period, which is designed to address two of these unresolved issues by testing two fundamental hypotheses regarding DBS for TRD: (1) It is possible to elicit a repeatable immediate response, which then enables stimulus optimization/personalization, and (2) It is possible to achieve sustained therapeutic effects without stimulating continuously by implementing a closed-loop DBS paradigm where stimulus is triggered by an iEEG biomarker of depression severity. They have so far enrolled 4 subjects in the study and the results indicate that: (1) immediate therapeutic antidepressant effects can be reliably and repeatedly elicited with

stimulation for at least one site/parameter set; and (2) DBS when delivered intermittently as part of a closed-loop paradigm where stimulus is delivered driven by a personalized iEEG biomarker of depression severity can lead to sustained antidepressant effects. These findings support the argument that acute neural signatures of TRD can be used to drive DBS.

Features essential for future DBS devices

Despite some technological innovations, current neurostimulators are essentially unchanged since the inception of contemporary DBS, still employing open-loop fixed-frequency constant stimulation. Yet insights into mechanisms and effects of therapeutic stimulation, a greater understanding of disease pathophysiology, and advances in engineering have raised the prospect of delivering truly novel neurostimulators in the near future (Guidetti et al., 2021).

Brain sensing

Brain sensing is amongst the most important features to include in neurostimulators, both because of the value of sensing and the prospect of providing dynamic, responsive therapy. The rationale includes: (1) Pathophysiology of disease: disease, symptoms, and disease-related oscillatory changes are dynamic, making dynamic monitoring valuable (O'Keeffe et al., 2020; Xiao et al., 2023); (2) Therapeutic mechanisms of DBS: DBS modulates brain oscillations, making brain sensing a sensible means of monitoring therapy dosing and efficacy (Arlotti et al., 2018); (3) Need for biomarker-guided therapy: while DBS for movement disorders has an immediate measurable therapeutic response, emerging DBS indications (e.g., depression) require biomarkers to judge therapeutic efficacy on a timescale relevant for programming; (4) Improved efficacy: evidence suggests aDBS may be superior to contemporary DBS (Little et al., 2013; Swann et al., 2018; Cagle et al., 2022); (5) Safety: responsive neurostimulation offers the prospect of reducing stimulation and thereby reducing off-target side effects (Little et al., 2016; Rosa et al., 2017); and (6) Chronic/remote monitoring: sensing can provide chronic and remote sensing of therapy and patient state, to enhance overall patient care and therapy. Beyond brain sensing, the field may ultimately benefit from integrating other sensors as well, including both physiological [e.g., autonomic, heart rate (Huang et al., 2022)] and behavioral measures (e.g., activity).

Alternative stimulation patterns

Almost all clinical use of DBS has involved the delivery of biphasic square wave stimulation at a constant frequency and a constant interpulse interval. The capability to deliver bursts of stimulation pulses at customizable frequencies and customizable interpulse intervals would help the field leverage promising findings from animal work and early human work. Optogenetic experiments have identified stimulation patterns that include variable interpulse interval, as capable of providing more cell type selective stimulation, or better treatment of specific motor signs in movement disorders (Spix et al., 2021). Theta burst stimulation may be more plasticity-inducing than standard constant frequency stimulation. Several human clinical trials of theta burst stimulation have suggested benefit in individual cases (Horn et al., 2020; Sáenz-Farret et al., 2021), but long term use of theta burst stimulation has not been investigated. Coordinated reset stimulation was introduced in animal models and has the potential to provide long lasting effects in the absence of ongoing stimulation (Tass, 2003; Tass et al., 2012). However, coordinated reset stimulation has only been tested in one human trial with externalized leads (Adamchic et al., 2014). Delivery of individual pulses time locked to the phase of a field potential oscillation could selectively reduce or enhance particular frequencies for therapeutic benefit (Cagnan et al., 2017). The lack of evidence in humans for efficacy of alternative stimulation patterns may be related to the limited capability of contemporary commercial DBS devices to deliver variable patterns.

Neuroimaging and DBS fiber-filtering

One prominent avenue to personalize DBS surgery and programming that has been proposed lies in gathering individual high quality MRI datasets that include diffusion-weighted imaging scans for tractography or specialized MRI sequences that allow for a better visualization of the DBS target (Neudorfer et al., 2022). An alternative strategy was recently proposed that involves three consecutive steps (Hollunder et al., 2021). The first involves identifying networks that, when stimulated, respond by modulating specific symptoms (such as tremor, bradykinesia, rigidity, or axial symptoms in the case of Parkinson's disease). Notably, and slightly counter-intuitively, these networks would be identified on a group level in a normative atlas space, e.g. using DBS network mapping (Horn et al., 2017) or DBS fiber filtering [Figure 10; (Baldermann et al., 2019; Li et al., 2020)]. In a second step, the normative networks could be reidentified in the individual patient by using individual tractography data, a process referred to as "template-matching" (Hollunder et al., 2021). The last step involves weighting the networks in a fashion that personalizes to the individual patient, termed "network-blending". For instance, in a patient with predominant tremor, the tremor network would receive a strong weight and would be considered more strongly than the networks that respond to other symptoms. The resulting weighted blend of networks may define (i) a programming target for existing leads that have already been implanted, or, after successful establishment of the approach, (ii) a personalized and refined surgical target within established DBS target nuclei.

Conclusion

The 11th Annual DBS Think Tank meeting facilitated productive discussions surrounding advances in neuromodulation research and the latest commercially available technologies. Translational research performed in animal models with

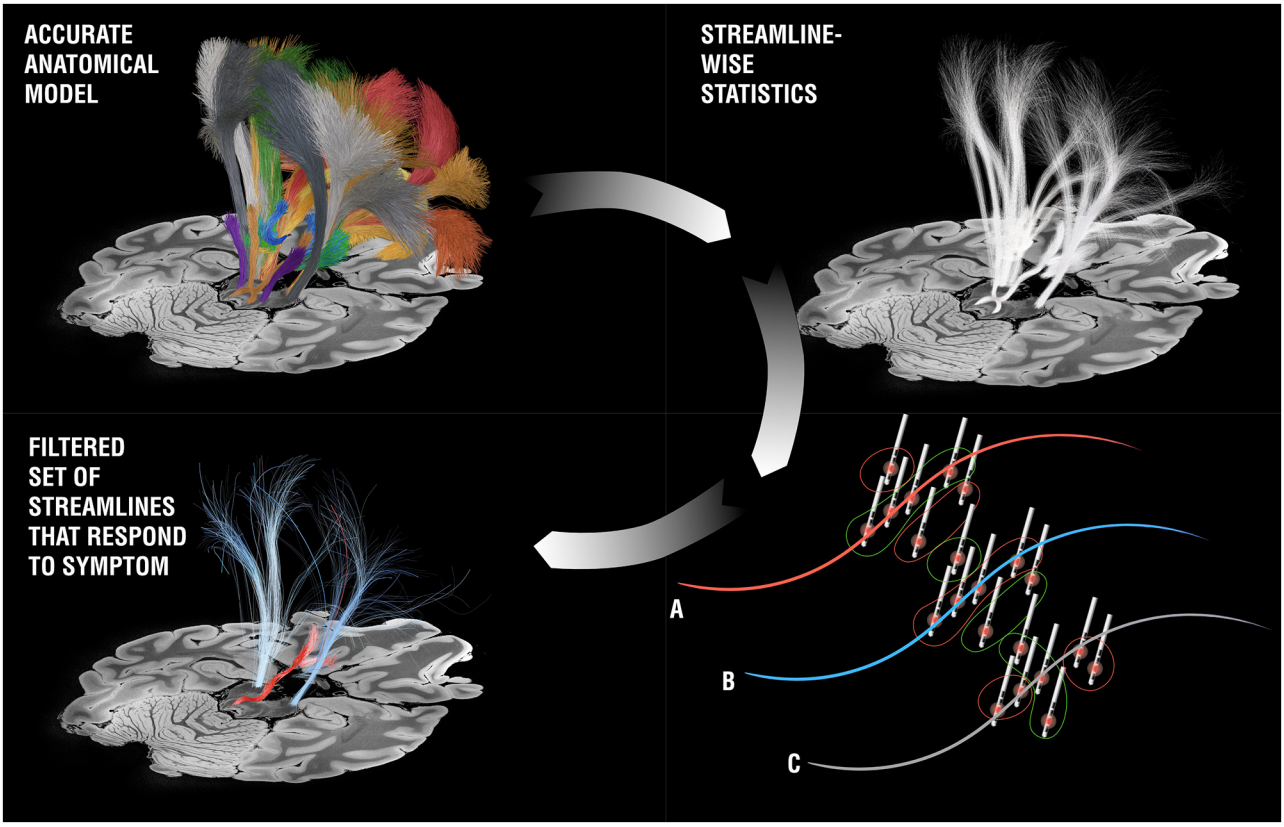

FIGURE 10
DBS fiber-filtering. Based on an anatomical model [pathway atlas or normative connectome, the basal ganglia pathway atlas (Petersen et al., 2019) is shown as an example, top panels], each streamline is selected and set into relationship with DBS stimulation volumes from a cohort of patients in a mass-univariate statistical approach. For each streamline, three general scenarios may result: **(A)** The streamline was predominantly modulated in patients in which a symptom of question was reduced, but less in patients in which the symptom deteriorated or stayed stable. If this is the case, a positive score is assigned to the streamline (these streamlines have been visualized with red color in most publications). **(B)** The opposite case: The streamline was predominantly modulated in the patients in which a symptom got worse (the tract receives a negative score and is often shown in blue). **(C)** There is no clear relationship between modulation of the streamline and changes of the symptom of question. In this case, the streamline is filtered out. When iteratively applied across all streamlines in the atlas, the bundles coding for improvements of a specific symptom can be identified (here the cerebellothalamic pathway for tremor improvement in right-lateralized DBS electrodes).

optogenetics and VNS and in humans with functional neuroimaging and neurophysiology shows promise to shed light on the potential mechanisms underlying DBS in a variety of disorders. Additionally, neurophysiological markers are increasingly being evaluated as control signals for aDBS as the next-generation paradigm to improve efficiency and efficacy. Tailoring aDBS algorithms to account for sleep and circadian patterns was a key point of discussion. Current commercially available technologies feature chronic sensing, imaging- and outcomes-guided DBS programming algorithms, digital health integration and cloud-based management systems, responsive stimulation for emerging epilepsy indications, the use of biosensors to guide the treatment of Parkinson's disease, and a commercial aDBS device. Additionally, many discussions focused on developing and evaluating neurophysiological and imaging markers to guide DBS for neuropsychiatric indications, such as OCD, TS, and depression. Attendees expressed unanimous support for an aggressive immediate solution for providing enhanced access to DBS devices to smaller and more rare indications. Despite many technological and research advancements, the field of DBS is at a crossroads, and the use of AI and data-driven approaches will likely be key to advance DBS as a widespread therapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Individual Academic Institutions. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in the studies. Animal studies were approved by individual institutional animal welfare committees at the respective academic institutions. All studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

KJ: Writing – original draft, Writing – review & editing. ND: Writing – original draft, Writing – review & editing. EG: Writing – original draft, Writing – review & editing. CW: Writing – original draft, Writing – review & editing. KW: Writing – original draft, Writing – review & editing. HB-S: Writing – original draft, Writing – review & editing. VV: Writing – original draft, Writing – review & editing. TM: Writing – original draft, Writing – review & editing. YS: Writing – original draft, Writing – review & editing. AM: Writing – original draft, Writing – review & editing. GL-M: Writing – original draft, Writing – review & editing. TW: Writing – original draft, Writing – review & editing. AH: Writing – original draft, Writing – review & editing. RG: Writing – original draft, Writing – review & editing. JO'K: Writing – original draft, Writing – review & editing. AG: Writing – original draft, Writing – review & editing. W-JN: Writing – original draft, Writing – review & editing. SL: Writing – original draft, Writing – review & editing. NP: Writing – original draft, Writing – review & editing. SS: Writing – original draft, Writing – review & editing. AF: Writing – original draft, Writing – review & editing. AH-B: Writing – original draft, Writing – review & editing. RR: Writing – original draft, Writing – review & editing. LM: Writing – original draft, Writing – review & editing. YP: Writing – original draft, Writing – review & editing. DG: Writing – original draft, Writing – review & editing. SM: Writing – original draft, Writing – review & editing. LK: Writing – original draft, Writing – review & editing. HT: Writing – original draft, Writing – review & editing. HB: Writing – original draft, Writing – review & editing. MP-N: Writing – original draft, Writing – review & editing. BS: Writing – original draft, Writing – review & editing. LC: Writing – original draft, Writing – review & editing. CM: Writing – original draft, Writing – review & editing. NH: Writing – original draft, Writing – review & editing. HM: Writing – original draft, Writing – review & editing. AK: Writing – original draft, Writing – review & editing. NP: Writing – original draft, Writing – review & editing. PS: Writing – original draft, Writing – review & editing. KF: Writing – review & editing. MO: Writing – review & editing. JW: Writing – review & editing.

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ND has a financial interest in Turing Medical Inc. and may financially benefit if the company is successful in marketing FIRMM motion monitoring software products, may receive royalty income based on FIRMM technology developed at Washington University School of Medicine and Oregon Health and Sciences University and licensed to Turing Medical Inc, and is a co-founder of Turing Medical Inc. These potential conflicts of interest have been reviewed and are managed by Washington University School of Medicine. AH reports lecture fees for Boston Scientific and is a consultant for FxNeuromodulation and Abbott. RG is an employee of Rune Labs. JO'K is CEO and Founder of Machine Medicine Technologies. W-JN received honoraria for consulting from InBrain – Neuroelectronics that is a neurotechnology company and honoraria for talks from Medtronic that is a manufacturer of deep brain stimulation devices unrelated to this manuscript. SL has received speaking honoraria from Medtronic and is a consultant for Iota Biosciences. SS is a consultant for Zimmer Biomet, Neuropace, Koh Young, Boston Scientfic, Sensoria Therapeutics, Varian Medical; co-founder for Motif Neurotech.

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Modeling the volume of tissue activated in deep brain stimulation and its clinical influence: a review

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Deep brain stimulation (DBS) is a neuromodulatory therapy that has been FDA approved for the treatment of various disorders, including but not limited to, movement disorders (e.g., Parkinson's disease and essential tremor), epilepsy, and obsessive-compulsive disorder. Computational methods for estimating the volume of tissue activated (VTA), coupled with brain imaging techniques, form the basis of models that are being generated from retrospective clinical studies for predicting DBS patient outcomes. For instance, VTA models are used to generate target-and network-based probabilistic stimulation maps that play a crucial role in predicting DBS treatment outcomes. This review defines the methods for calculation of tissue activation (or modulation) including ones that use heuristic and clinically derived estimates and more computationally involved ones that rely on finite-element methods and biophysical axon models. We define model parameters and provide a comparison of commercial, open-source, and academic simulation platforms available for integrated neuroimaging and neural activation prediction. In addition, we review clinical studies that use these modeling methods as a function of disease. By describing the tissue-activation modeling methods and highlighting their application in clinical studies, we provide the neural engineering and clinical neuromodulation communities with perspectives that may influence the adoption of modeling methods for future DBS studies.

KEYWORDS

volume of tissue activated, VTA, deep brain stimulation, DBS, neuroimaging, probabilistic stimulation atlas, connectivity maps

1 Introduction

Deep brain stimulation (DBS) is a neuromodulatory therapy that has been used to treat various neurological disorders for over 40 years. DBS was first introduced throughout the late 1980s and 1990s by Benabid and colleagues as an alternative to lesional surgery for treating medication refractory Parkinson's disease (PD) (Benabid et al., 1989, 1991, 1996, 1998; Benazzouz et al., 2000). In 1997, the FDA approved the use of thalamic DBS to treat PD tremor and essential tremor (Aum and Tierney, 2018) and the adoption of neuromodulation for movement disorders spread quickly soon after. Following its success in treating motor

symptoms, DBS was studied for its utility in treating psychiatric disorders, beginning in 1999 when Nuttin and colleagues examined the impact of DBS in four patients with obsessive-compulsive disorder (OCD) (Nuttin et al., 1999). Over the last few decades, the FDA further approved the use of DBS for OCD and epilepsy (Nuttin et al., 1999). Currently, researchers are exploring the use of DBS for other psychiatric disorders, such as Tourette syndrome, major depressive disorder, eating disorders, substance use and addiction, chronic pain, tinnitus, Alzheimer's disease, and anxiety disorder (Lee et al., 2019).

DBS is rapidly growing as a neuromodulatory therapy for many medication-refractory neurological diseases and it is estimated that by 2019 over 160,000 people had received DBS world-wide with a projected growth of more than 12,000 new implants per year (Lee et al., 2019). DBS can be very effective in select patients with fewer adverse events compared to traditional lesional procedures. DBS has progressively entered the clinical sphere as a predominant and effective solution for medication-resistant and refractory motor and psychiatric conditions (Mayberg et al., 2005; Greenberg et al., 2006; Schlaepfer et al., 2008; Malone et al., 2009; Parastarfeizabadi and Kouzani, 2017).

Methods to optimize the clinical benefit of DBS for individuals with various diseases are a major topic of current research in the field of brain neuromodulation therapy. Data-driven models made from retrospective studies of populations of patients are beginning to allow for more precise clinical guidance on surgical placement of DBS leads and programming of stimulation parameters of the electrodes (Wong et al., 2020). However, as more practitioners adopt the available methods, it becomes increasingly important for the community to understand their limitations and assumptions. The modeling tools including those that predict the extent of tissue activated by the stimulation (i.e., volume of tissue activated (VTA)) and its corresponding use in neuroimaging procedures that make it relevant to disease target structures or connected networks fall within this scope. By contextualizing VTA in the history of neuromodeling with respect to DBS and by analyzing how it works, we can demystify its function in an attempt to improve understanding for use in future clinical studies and practices. Similarly, by analyzing instances in which VTA with neuroimaging has been used clinically, we may extract its use in the progression of DBS therapy and identify areas in which advances in modeling are needed.

1.1 Overview of the VTA and its use with neuroimaging

The VTA approximates the spatial extent of the modulatory influence of a voltage field arising from stimulating electrode/s on neighboring neural tissue. It is visualized as a volume and is a useful metric with which to compare overlap with specific anatomical brain structures or fiber tracks connecting distant brain regions. This volume does not accurately represent the microscopic biophysical reality of cell-specific activation near the DBS lead; however, it has become a very useful tool for the study and prediction of clinical impact of DBS therapy. How the volume is calculated and the differences that lie there-in are discussed in Section 2.

The utility of the VTA is dependent on imaging the brain. Wårdell et al. provide a detailed review of imaging and modeling technologies for DBS (Wårdell et al., 2022). In short, the DBS lead location with respect to anatomical structures of the individual must be identified with pre-operative MRI for anatomy and post-operative MRI or CT scans for lead localization. Existing neurological atlases then need to be warped to the patient's brain images to provide spatial reference points (Wårdell et al., 2022). Additionally, pre-operative MRI scans with diffusion tensor imaging (DTI) provide extra information that can be used to define local anisotropic tissue electrical conductivity values that can inform the VTA calculation (Tuch et al., 2001; Butson et al., 2007). This additional specificity can make for a more accurate VTA estimation, especially when patient-specific data is used (Malaga et al., 2021, 2023). However, DTI methodological parameters including voxel size and resolution can introduce error (Rodrigues et al., 2018). For example, when using VTA models that do not assume a uniform and homogenous tissue, the acquisition quality and parameters of the DTI sequences can impact the resulting distribution of the electric field and ultimately the shape of the VTA.

1.1.1 Target-based stimulation mapping

The initial use of VTA calculations, besides its role in the design and characterization of electrode/lead geometries (Butson and McIntyre, 2005b), was to determine to what extent target brain structures were affected by the electrical stimulation through viewing the overlap between the predicted VTA and the anatomical structure (McIntyre et al., 2004b), as depicted in Figure 1A. This vein of research has evolved into using data-driven approaches (Figure 1B), where populations of patient data provide probabilistic estimates of DBS efficacy and are used to help define optimal "sweet spots" for stimulation targets (Butson et al., 2011; Cheung et al., 2014; Eisenstein et al., 2014; Dembek et al., 2017; Reich et al., 2019). Different approaches have been used to cluster the patient data for development of probabilistic maps of stimulation efficacy, including using thresholding or voxel-wise statistical methods. Dembek et al., suggest that voxel-wise statistics that base outcome in a certain voxel against average clinical outcomes is a promising method in that it provides the most consistent results for different scenarios (Dembek et al., 2022). Other work highlighting the influence of nuances in methods within voxel-wise statistical approaches (Nordin et al., 2022) shows that this facet of DBS research is also still being refined. Probabilistic stimulation maps for prospective use in which an individual's predicted VTA may be tuned via stimulation parameter selection for optimal mapping to a disease-specific probabilistic stimulation atlas will enable optimization for stimulation programming and lead placement and may reduce the amount of clinical trial and error.

1.1.2 Network-based stimulation mapping

Alternatively, to get a better understanding of the underlying mechanisms of DBS with respect to network activity, researchers introduced techniques of using the VTA to seed calculations that determined which distant brain regions were either structurally or functionally connected to the stimulation site. For example, DTI information can be used to reconstruct and approximate axonal fiber tracts that reveal *structural* network connectivity throughout the brain (Horn et al., 2014). In this method, representations of individual fiber tracts that pass through the VTA are identified and traced to cortical or other distant brain areas (Figure 2A). Additionally, another method correlates the blood-oxygen-level-dependent (BOLD) brain signal at the voxel level via whole brain functional MRI (fMRI) with voxels within the VTA to identify distant regions that are *functionally*

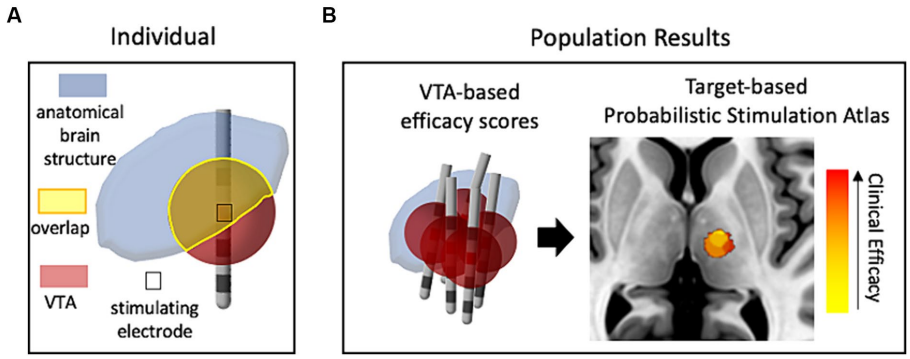

FIGURE 1
The use of VTA and structural neuroimaging in clinical retrospective studies. **(A)** Conceptual drawing of one patient's VTA calculation compared (voxel-wise) with a neuroanatomical atlas to estimate the influence of stimulation on target structures. **(B)** Representative probabilistic results from a population of patients that show correlation of VTAs with clinical outcomes (efficacy of treatment with minimal side-effects). Red denotes high correlation with clinical efficacy while yellow denotes low correlation. The image of the brain was taken from standard template image (MNI 152 brand).

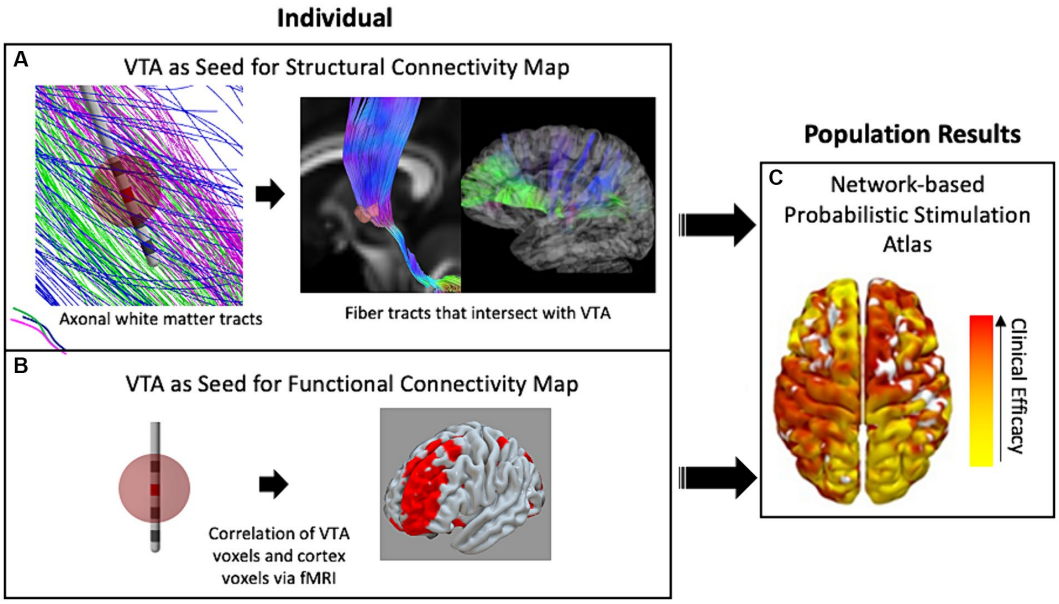

FIGURE 2
The use of VTA and connectivity mapping in retrospective studies. **(A)** White-matter fiber tracts intersecting the VTA enable estimation of connectivity with distant brain regions including the cortex. **(B)** The fMRI voxels included in the VTA are correlated with whole-brain fMRI to map functional connectivity in a single individual. **(C)** Either technique for connectivity mapping may be used in retrospective studies of populations of patient groups to result in a data-driven network-based connectivity atlas for a specific disease. Red denotes high correlation with clinical efficacy while yellow denotes low correlation.

connected to the VTA area (Al-Fatly et al., 2019). The two methods are conceptually depicted in Figure 2. Both methods may be used within a population study to result in independent network-based stimulation atlases/maps. VTAs can also be used to compute these network metrics at a cohort level within a framework known as a "connectome." A connectome represents group-averaged structural or functional connectivity data that can either be patient-and disease-specific or normative—meaning a standardized dataset generated from a large collection of healthy volunteers.

In summary, VTA computations in conjunction with advanced neuroimaging has allowed for much insightful information to be gleaned from population-based retrospective studies. The field is on the verge of being able to use the results of these studies to perform clinical predictions that could aid in the presurgical planning of lead placement and reduce programming time after implantation. This technology will enable clinician guidance that is individualized to each patient. However, as precision is necessary for patient-specific applications, the errors and assumptions within the modeling methods need to be fully understood. In this review, we highlight key differences in the methodologies and biophysical foundations of current VTA models (Section 2), identify the VTA/neuroimaging models used in a collection of disease-specific clinical studies (Section

3), and comment on trends and use-cases (Section 4). The errors and biases found in the methods for target-or network-based stimulation mapping are not discussed in detail in this review.

2 Calculating the VTA

DBS stimulation hardware provides rectangularly shaped stimulus waveforms, which may be voltage or current-controlled (Amon and Alesch, 2017). However, traditionally, voltage-controlled waveforms have been used clinically and thus many of the VTA approximation methods are based on voltage input parameters. The waveform is in the form of pulse trains with pulse width on the scale of tens to hundreds of microseconds and pulse frequency in the low hundreds of Hz (Volkmann et al., 2006). These stimulation (or programming) parameters including pulse shape (such as monophasic or biphasic) are needed to define the VTA around one or multiple stimulating electrodes. Frequency has been shown to have minimal effects on the physics-based calculation of the VTA (Duffley et al., 2019) and thus is usually neglected in VTA estimation methods. Different electrode configurations such as monopolar (i.e., one stimulating electrode with respect to a distant ground electrode), bipolar (one stimulating electrode with respect to an adjacent ground electrode), or multiple monopolar are also possible. Figures 3A,B capture these parameters. Figure 3A shows examples of monophasic and biphasic stimulus waveforms with negative (cathodic) leading pulses and Figure 3B shows examples of monopolar or bipolar electrode configurations on a typical DBS lead (such as the Medtronic 3387 lead) with four cylindrical electrode contacts. In the monopolar configurations, the ground contact is the internal pulse generator (IPG) and is usually modelled as the outer boundary in FEM simulations (Butson and McIntyre, 2005b; Aström et al., 2009).

Existing research-grade, commercial, and open-source simulation toolboxes that couple the VTA estimations with neuroimaging data employ a variety of methods to compute the VTA. As a result, the term "VTA" has taken on several definitions across the literature and commercial platforms. Each VTA model has inherent assumptions and limitations, which may make one model more appropriate than another for certain clinical DBS studies. In this section, we will highlight the major assumptions and limitations for the major VTA approaches; but first we present historical context with respect to modelling neural activation and DBS.

2.1 Modeling neural activation—historical context

Computational models used to predict neural excitation have evolved considerably since 1907 when Louis Lapicque first described the integrate-and-fire model (IF) as a tool to simulate the spiking activity of neuronal membranes using a parallel capacitor and leak resistor (Abbott, 1999). Hodgkin and Huxley provided a more complex equivalent circuit model of the cell membrane of the squid giant axon that incorporated the dynamics of specific ion-channels constituting the action potential (Hodgkin and Huxley, 1952). Incorporating a Hodgkin and Huxley-style membrane model, Wilfrid Rall developed a mathematical model by which to simulate the electrophysiology of realistic morphologies of neurons including the soma, dendritic tree, and axon (Rall, 1962). Using cable and core-conductor theory (Rall, 2011), his work set the stage for multi-compartment cable models of neurons and axons that are widely used today in computational neuroscience.

Regarding DBS, multi-compartment cable models were first used to try to elucidate the therapeutic mechanism of action of the stimulation. Four theories were tested with biophysically accurate models of thalamocortical relay neurons (including soma, dendrites, and axon) (McIntyre et al., 2004a). Of the four theories, three hypothesized that electrical stimulation inhibited neuronal responses through (1) blockade of voltage-gated currents in the neurons, (2) synaptic inhibition of neurons, or (3) synaptic transmission failure due to transmitter depletion. The fourth theory suggested that electrical stimulation directly modulated the pathological network activity via modulation of surrounding neural tissue—an informational lesion. McIntyre et al. showed that physics-based computational modeling results compared with functional imaging and neural recording suggest that the fourth theory is most probable (McIntyre et al., 2004a,c). However, there is still much ambiguity in the biological mechanisms that underlie the effectiveness of DBS for various diseases (Lee et al., 2019). Nevertheless, computational modeling studies also showed that the axon (or "fiber of passage") was most important to model since it could be most easily depolarized by electrical stimulation and was the primary conduit for action potential propagation (McIntyre et al., 2004a,c). Based on these findings, researchers began to use modeling to predict an approximated volume of tissue activated (VTA) surrounding the active DBS contact as a function of stimulation parameters. Since biophysically accurate, physics-based models are computationally expensive and require specific computing skills, methods to calculate a VTA manifested in a myriad of flavors with different levels of approximations.

2.2 FEM-based models

Generally, a top-level distinction can be drawn between VTA methods that either need an extra computational tool that uses the finite element method (FEM) to compute the voltage field and/or its spatial derivatives as input to its VTA model, or ones that do not (Figure 4). The papers referenced in Figure 4 and described in Sections 2.1–2.3 are the seminal papers describing new VTA methods or new increments to known methodologies; it is not intended to be comprehensive of all papers published on VTA methods.

The finite-element method is commonly used to numerically solve for the voltage field, V, resulting from a stimulating electrode in a 3-dimensional conductive medium defined by conductivitys σ, which can be real or complex to incorporate frequency dependence in a tissue model (i.e., capacitive effects). The differential equation solved by FEM tools to calculate the VTA is the Laplace equation:

$$\nabla \cdot \sigma \nabla \mathbf{V} = \mathbf{0}, \tag{1}$$

with boundary conditions that reflect the stimulation voltage or current at electrode contacts. FEM-based models are dependent on the physical parameters that incorporate the geometry of the DBS lead, tissue heterogeneity and anisotropy, and the presence of

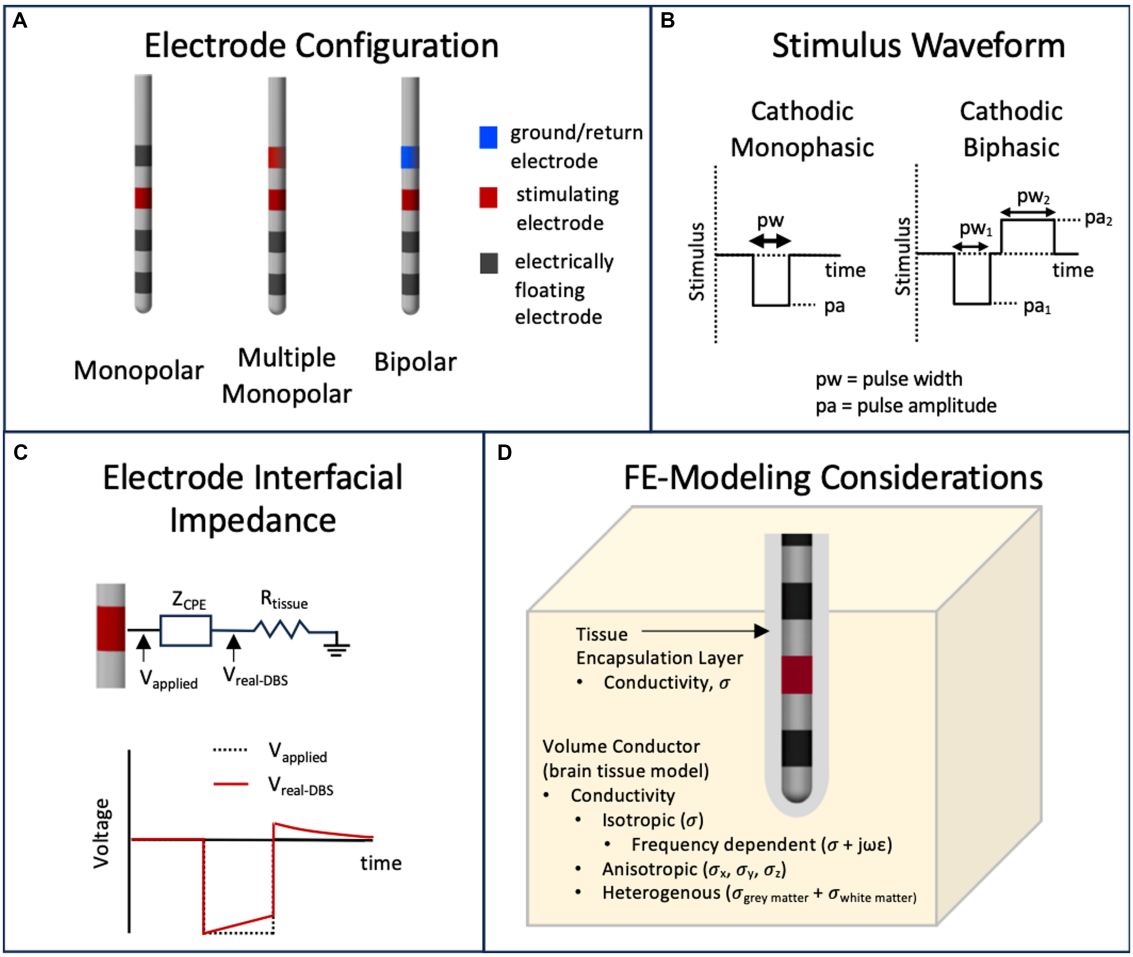

FIGURE 3
Parameters that influence the calculation of the VTA. **(A)** Typical DBS leads can have various stimulating electrode configurations including monopolar, bipolar and multimonopolar. **(B)** Typical stimulus waveforms consist of cathodic monophasic or cathodic biphasic voltage controlled or current controlled pulses with user defined pulse amplitude and pulse width. **(C)** The capacitive nature of the electrode interface, usually modeled as capacitor or a constant phase element (CPE) will filter a voltage-controlled stimulus pulse. **(D)** The volume conductor in a finite element model can have materials that model the brain tissue and tissue encapsulation layer with various representations of electrical conductivity.

encapsulation tissue around the lead due to a foreign body immune reaction. Figure 3D depicts these parameters. Typically, these FEM simulations are time-independent and thus the time dependence of the voltage waveform (Figure 3A) or nonideal capacitive effects of the electrode/electrolyte interface (Brug et al., 1984; Butson and McIntyre, 2005a; Miocinovic et al., 2009) as seen in Figure 3C are not modeled in the FEM simulation. Time-dependent effects—the capacitively filtered stimulus waveform and the programming parameter pulse width—are usually taken into account using separate methods (e.g., incorporated into the equivalent circuit-based field-axon simulation), but can be incorporated in FEM simulations using Fourier methods; e.g., the OSS-DBS simulation framework has this capability (Butenko et al., 2020).

As a secondary distinction between VTA methods within the FEM branch (Figure 4), FEM-derived values of the voltage field are used to compute the VTA via heuristic models or ones derived from multicompartment axon models (i.e., field-axon). Field-heuristic models, discussed in the following section, couple a FEM solution of field values (i.e., 1st spatial derivative of the voltage field) with clinical data of DBS effectiveness.

2.2.1 Field-heuristic

With least computational complexity out of the FEM-based models, field-heuristic VTA models use computational methods to define iso-contours or iso-surfaces of electric field values that correlate with perceived clinical efficacy. Hemm et al. first introduced this method to help visualize the extent of the VTA by correlating calculated 2D field contours with MR brain images and therapeutic DBS parameters in patients with leads in the internal globus pallidus (GPi) for dystonia therapy (Hemm et al., 2005a,b). They used a homogenous, isotropic tissue conductivity model and surmised that for numerous patients using monopolar, double monopolar, or bipolar electrode configurations, the absolute value of electric field vector of 0.2 V/mm was a good estimate of GPi coverage.

Aström et al. further evaluated this method of using the computed electric field in an FEM model and a heuristic threshold value of 0.2 V/mm to help visualize a VTA using a heterogenous tissue model (Aström et al., 2009). Their paper states that "[this method] should only be interpreted as a boundary of tissue, where the electric field (absolute value of the 3D vector) is 0.2 V/mm or larger, and not as the

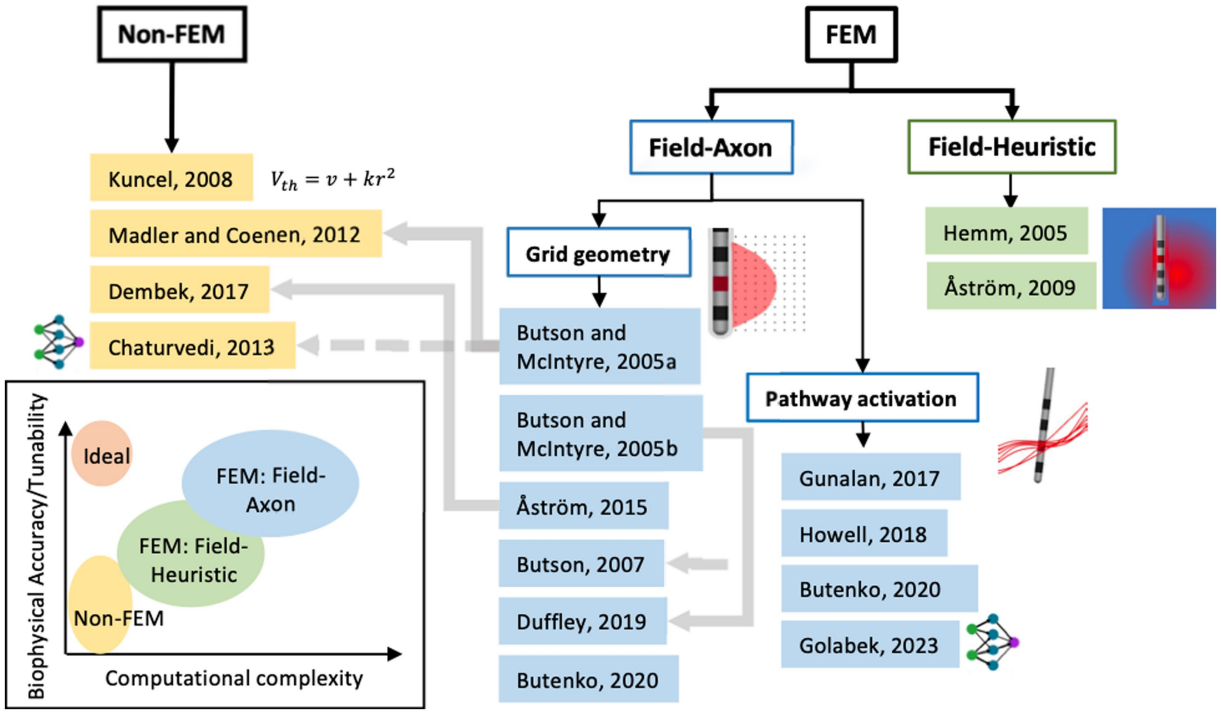

FIGURE 4
Classification of seminal papers on modeling methods for volume of tissue activated or pathway activation based on using finite-element methods (FEM) or not. Further classification can be made with axon biophysical models (field-axon) or not (field-heuristic) and then an even further classification between axons placed on a grid in conventional VTA and axons defined by tractography. The grey lines denote dependence of one model on the former. The groups of models can be assigned levels of computational complexity and biophysical accuracy or tunability as seen in the chart (bottom left).

volume of tissue influenced by the stimulation," but nonetheless was used to help explain stimulation-induced side effects of DBS for Parkinson's disease therapy in one patient. The FEM model was used to compute the maximum electric field in 3D space with a heterogenous model space of white and grey matter (σ = 0.06, 0.09 S/m, respectively) based off of patient-specific MRI data and with normalized stimulus voltages (reduced by a factor 0.89) to accommodate for non rectangular stimulus waveforms from the IPG (Butson and McIntyre, 2007), but no tissue encapsulation was modeled. The 0.2 V/mm threshold value was based off of two clinical inferences: (1) the isolevel of 0.2 V/mm was within a clinically effective radius of 2–5 mm in the STN as given by (Volkmann et al., 2006) for Parkinson's disease therapy using conventional monopolar programming and (2) Hemm's early work with calculated electric field values and GPi stimulation for dystonia (Hemm et al., 2005a,b).

Choosing a single electric field threshold to compute a volume is inherently dependent on the FEM model parameters (e.g., tissue conductivity, heterogeneity, etc.) and thus prone to large variability, plus that it does not take into account time dependency on stimulus waveforms. However, many clinical studies (referenced in Section 3) use the 0.2 V/mm electric field threshold as a VTA metric as it is a straight-forward method.

2.2.2 Field-axon—grid geometry

The other types of FEM models couple field information to multicompartment models of myelinated axons. One subset of these models place axons in a grid perpendicular to the long axis of the DBS lead (i.e., grid geometry) and estimate a volume based on the extent of activation of individual axons at certain stimulation parameters (e.g., voltage, pulse width, and sometimes pulse train frequency and capacitive effects of the tissue or electrode interface that shape the waveform). Another subset of field-axon models, pathway activation models, make use of more realistic axon pathways via MRI-based tractography (Coenen et al., 2012) and will be discussed in more detail in Section 2.2.3.

Butson and McIntyre (2005a) developed the first of the grid-geometry field-axon models. Building on earlier work (McIntyre et al., 2004b), they performed a simulation study that used multicompartment models of a 5.7 mm diameter myelinated axon (McIntyre et al., 2002) to predict action-potential excitation from monopolar cathodic stimulation of a Medtronic 3387/3389 DBS electrode for a single pulse width of 90 µs over a range of isotropic tissue conductivities and encapsulation conductivities. Fibrotic tissue encapsulation was modelled in the FEM model as a space adjacent to the lead with a range of lower conductivities (by a factor of 2, on average) than the bulk tissue. In subsequent work (Butson and McIntyre, 2005b), Butson and McIntyre again used the same 5.7 mm myelinated axon grid-model to predict activation for multiple pulse-width cathodic monopolar signals in a homogeneous isotropic medium with conductivity equal to 0.3 S/m; however, their goal was to define an analytical equation fit to their simulation results that would decrease the time and computational complexity of VTA prediction. They make use of the activating function (Rattay, 1986), which is the second spatial derivative of voltage ($\nabla^2 V$), and shown to

be a useful value to define a threshold since it is relatively constant over a range of electrode designs (Butson and McIntyre, 2005b). Their result was a response curve of activating function thresholds for the individually placed axons as a function of the product of stimulus amplitude and pulse width. Because of their axisymmetric simulation, a 2-D contour line based on an activating function value for specific stimulus voltage amplitude and pulse width parameters can be rotated around the lead to define the 3-D VTA. Their work instantiated a look-up-table (LUT) approach for fast prediction of VTAs based on stimulation parameters (pulse amplitude and width). The 2005b model was limited in that only isotropic media with conductivity of 0.3 S/m was used in the FEM, and thus does not apply in heterogeneous and anisotropic models. Cicerone (Miocinovic et al., 2007), an academic software coupling VTA with neuroimaging software that has been commercialized by Boston Scientific as GUIDE, uses precompiled data from simulations using methods from the above studies to provide fast computation for a number of monopolar electrode settings. The effects of electrode interfacial impedance (Butson and McIntyre, 2005a) are incorporated in Cicerone.

In an effort to compare electric field thresholds with activating function thresholds and to analyze the effect of other considerations such as fiber diameter, Åström et al. used multicompartment cable models coupled with FE modelling (Åström et al., 2015). Their model used slightly different biophysical parameters for the axon model than used by the Butson-McIntyre models and employed a single cable model instead of a double cable model; however, the fibers were similarly placed in a grid perpendicular to the DBS lead. Also, the FEM simulation used an isotropic conductivity of 0.1 S/m in the volume conductor. Their study suggested that isosurfaces generated by electric field thresholds and activating thresholds could be used to approximate the VTA defined by field-axon simulations. They also show that the electric field (1st spatial derivative of voltage) rather than the activating function (2nd spatial derivative) is a simplified metric by which to define VTA threshold values, supporting their earlier work (Aström et al., 2009) because it is largely independent of stimulation amplitude for large diameter fibers for a specific pulse width. Thus, their method when used for fast prediction, could also entail a look-up table approach with computation of the electric field to estimate the VTA for a stimulus of a specific pulse width, only. Of note, their results for a fiber diameter of 3.5 mm matched simulation results for the Butson-McIntyre 5.7 mm diameter model. The nodal spacing, which turned out to be a large factor in excitability, was similar for the individual axon models of the mentioned diameters. Two opensource packages use these results for fast computation. Lead DBS (Horn et al., 2014) and FastField (Baniasadi et al., 2020) compute VTAs from electric field isocontours based on data from Table 3 in Åström et al. (2015) for cathodic pulse widths of 30, 60, 90, and 120 µs and fiber diameters from 2 to 5 µm. In these cases the average electric field value, which corresponds to a voltage pulse amplitude of 3 V, is used as the VTA threshold metric.

One limitation of grid-geometry models is that isotropic tissue conductivity must be used since the volume is defined by revolving the contour created by individual fiber activation in the plane grid-geometry. Later work by Butson et al. using the activating-function threshold approach showed that these models can be adapted to accommodate anisotropic tissue conductivities, defined by DTI, and create 3D surfaces informed by the local conductivity (Butson et al., 2007). How to best compute the second spatial derivative for a 3D volume was the topic of the latter two studies (Anderson et al., 2018; Duffley et al., 2019). The max eigenvalue of the Hessian matrix, which is the spatial partial second derivative of voltage, is used in these models to define a VTA volume that is independent of fiber orientation. Being that it uses the max value along any spatial direction, it could overestimate activation for realistic fiber trajectories; however, it is a very convenient method to use with anisotropic or heterogenous conductivity in FEM models. The absolute value of the 3D electric field vector can similarly be used to define a VTA within a finite-element model with local conductivities defined by DTI data; its estimation could also lead to overestimation.

2.2.3 Field-axon—pathway activation models

Pathway activation models (PAM) define the axon pathways, from either patient DTI-based tractography information or structural connectome and pathway atlas data sets, and are not technically VTA models, as activation of discrete fibers near the DBS electrode are computed rather than a volume. However, they do predict axon/fiber activation as a response of DBS and the methods used for these models fall under the field-axon classification (Figure 4). Gunalan et al. used detailed FEM models with multi-compartment axon models of 5.7 mm diameter to predict activation of axons in two corticofugal axonal pathways: the hyperdirect pathway and the internal capsule fibers of passage (Gunalan et al., 2017). Their modeling results correlated well with effective clinical stimulation settings in that a portion of the hyperdirect pathway fibers were activated and none of the fibers in the internal capsule were activated, which corresponded well with clinical hypotheses for efficacy.

Since multi-compartment axon models are computationally intensive, subsequent work by Howell et al. (2019) developed a linear approximation to the multi-compartment axon model that allowed for much faster prediction of FEM-informed pathway-activation models. They presented empirical models for a range of axon diameters. Additionally, Golabek et al. developed another pathway-activation fast-prediction method using an artificial neural-network model for the 5.7 mm diameter axon (Golabek et al., 2023).

Field-axon VTA or pathway activation models are ostensibly the most tunable for the specific application and thus can be made specific to patient MRI information, but the computational complexity can be a barrier to entry for many practitioners and clinicians.

2.3 Non-FEM-based models

Some VTA models do not need FEM computation as input. They are based on empirical clinical studies and/or rely on relationships derived from physics-based multicompartment axon models and thus are inherently specific to the data from which they were derived. However, because of not having to perform extra computation, these models are extremely fast; nevertheless, they may also introduce error to the study if used outside of their limits.

Kuncel et al. adapted an empirical model for neuron/axon activation that relates the threshold voltage to distance away from an electrode (threshold-distance relationship) for DBS for Parkinson's disease (Kuncel et al., 2008). The empirical model, which was first determined for excitation of pyramidal-cell tracts in the cat motor cortex (Stoney et al., 1968) is described in Eq. 2. It assumes that the

threshold voltage for excitation, V_{th}, (which would represent the amplitude of the applied voltage pulse) is proportional (with constant k) to the squared distance r from the electrode (which would represent the spherical radius of a volume of tissue activated) plus an offset v:

$$V_{th} = v + kr^2. \quad (2)$$

Kuncel et al. tuned the empirical model based on paresthesia-related side effects of monopolar (cathodic) stimulation in the Vim nucleus of the thalamus. The Kuncel model is specific to monopolar stimulation on a model 3387 Medtronic DBS lead, a 90 µs cathodic monophasic voltage pulse and comprises an average of results from 8 subjects. Also, the influence of tissue and electrode impedance is inherently built into this model. Interestingly, as shown in Åström et al. (2015), the Kuncel model is equal to an electric field threshold value of 0.165 V/mm in isotropic media of 0.1 S/m.

Mädler and Coenen (2012) introduced another empirical model computing the VTA via a spherical radius from the middle of a monopolar DBS electrode as a function of stimulus voltage amplitude (V_{th}) and electrode and electrode/tissue impedance by using the results of field-axon simulations in Butson and McIntyre (2005a). They fit a second order polynomial to the computational model results of the form:

$$V_{th}(r,\Omega) = k_0 + k_1 r + k_2\Omega + k_3 r^2 + k_4\Omega + k_4\Omega^2, \quad (3)$$

where r is the radius from the center of the electrode, k's are fitting constants, and W is the impedance of the system. Impedance values from Butson and McIntyre (2005a) were determined from *in situ* impedance measurement by the IPG stimulator at a frequency of 30 Hz. Also, this model is specific to 90 µs cathodic monophasic pulse trains. According to Åström et al. (2015), this model is equivalent to an electric field threshold of 0.19 V/mm in isotropic media of 0.1 S/m when using an impedance of 1,000 Ohms, which is very close to the heuristic value of 0.2 V/mm.

Dembek et al. established another simple model to estimate the spherical radius, r, of VTA fit to Åström et al.'s (2015) field-axon simulations that incorporate the effect of pulse width on electric field threshold (Dembek et al., 2017). Their model which is derived from Coulumb's law is as follows:

$$r = \left(\frac{pw_{real}}{pw_{given}}\right)^{0.3} * \sqrt{0.72\frac{I}{E_{given}}}, \quad (4)$$

where I is an applied stimulus current amplitude, pw_{real} is the pulse width of the applied pulse, and pw_{given} and E_{given} are reference values of known correlation between pulse width and electric field threshold values. Dembek et al. used the values of 0.165 V/mm and pulse width of 90 µs for the "given" parameters that matched the empirical results from Kuncel et al. (2008) with the Åström et al. (2015) model for electric field threshold. If the impedance of the system is known (e.g., through measurement via the IPG), then a voltage amplitude instead of current may be used in this model. The Dembek et al. (2017) model generalizes monopolar, cathodic monophasic stimulation to user specified pulse widths to easily calculate a VTA.

The last of the non-FEM models is one by Chaturvedi et al. (2013), which uses large-scale computational simulation results stemming from the methods of Butson and McIntyre (2005a) and Miocinovic et al. (2007) to train an artificial neural network to predict VTAs based on numerous user input parameters. The parameters include stimulus voltage amplitude, pulse width, high, medium, or low tissue encapsulation resistance, and electrode configuration (4 monopolar, 18 bipolar configurations). The training data consisted of FEM results using isotropic tissue conductivity of 0.2 S/m outside of the tissue encapsulation layer. This is the only non-FEM model able to accommodate bipolar electrode configurations.

2.4 Open-source, academic, and commercial simulation platforms

Providing the community with simulation tools that couple neuroimaging with VTA or pathway-activation calculation with reduced computational burden has been the intent of commercial and open-source platforms. Table 1 lists these simulation tools and their base VTA model and associated available user input parameters. All of these platforms stem from the academic works discussed in Sections 2.2–2.3 and many use simplified algorithms based on precomputed data from detailed field-axon simulation studies. Moreover, this table lists what type of neuroimaging/visualization capability is paired with VTA simulation (i.e., anatomical target structures and structural and functional network connectivity) within each tool.

Regarding open-source simulation packages, Lead-DBS, provides visualization of structural atlases as well as structural and functional network connectivity maps, gives the option to choose between four methods for VTA prediction, including three non-FEM models (Kuncel et al., 2008; Mädler and Coenen, 2012; Dembek et al., 2017) and a FEM-based field-heuristic LUT model representing data from Åström et al. (2015) and Horn et al. (2019). A more recent platform release by Lead-DBS includes field-axon grid-geometry and pathway-activation capability via the OSS-DBS simulation tool (Butenko et al., 2020; Neudorfer et al., 2023). FastField (Baniasadi et al., 2020) is another open-source toolbox with only co-visualization of structural atlases and VTAs, not network connectivity maps; but it provides extremely fast computation of electric fields via precomputed FEM models for a multitude of commercial monopolar or bipolar electrode configurations and fast computation of a VTA using an empirical model fit to data from Åström et al. (2015). Linköping University has an open-source modelling tool that combines an FEM solver, ELMA (Johansson et al., 2019), with a VTA and neuroimaging platform, DBviS (Wårdell et al., 2022). This tool allows for co-visualization of VTA surfaces with structural atlases and uses electric-field-heuristic VTA methods or VTAs defined by data from Åström et al. (2015) that observes the variability due to fiber diameter and stimulus pulse width. SciRun (SCI Institute, 2016) is an open-source platform from the University of Utah that couples an FEM solver with the biophysical solver Neuron (Hines and Carnevale, 2001) for modeling field-axon simulations. This tool may be combined with structural images or network connectivity atlases and is extensively used by the Butson research group. They also have developed simplified visualization programs that can be run on a tablet for fast computation and make

TABLE 1 Description of open-source, academic, and commercial VTA and neuroimaging visualization software platforms.

	Software platform	VTA method	Electrode type	Tissue/FEM parameters	Waveform parameters	Neuroimaging visualization with VTA
Open-Source	Lead DBS	Non-FEM: Kuncel et al. (2008), Mädler and Coenen (2012), Dembek et al. (2017)	Monopolar (Medtronic 3387, 3389)	See VTA method	Cathodic monophasic, 90 µs or variable pulse width; variable voltage amplitude	Anatomical target, structural network connectivity, functional network connectivity
		FEM: Field-heuristic or LUT based on Åström et al. (2015) data	Monopolar, bipolar	User-defined: variable heterogenous isotropic conductivity (grey/white matter)	Field-heuristic: voltage or current amplitude; LUT VTA parameters: cathodic pulse width 30, 60, 90, 120 µs, axon diameter (2–5 µm)	
		FEM: field-axon (Butenko et al., 2020)	User defined: any	User defined: any	User defined: any	
	FastField	FEM: Field-heuristic or algorithm based on Åström et al. (2015) data	Monopolar and multimonopolar for 12 electrodes from 4 different vendors	User defined: variable isotropic, homogeneous conductivity	Field-heuristic: voltage or current amplitude; LUT VTA parameters: cathodic monophasic, 30, 60, 90, or 120 µs pulse width, variable amplitude	Anatomical target
	ELMA+DBStim	FEM: Field-heuristic or LUT based on Åström et al. (2015) data	Monopolar, bipolar	Isotropic, heterogenous conductivity; with or without tissue encapsulation	Field-heuristic: voltage or current amplitude; LUT VTA parameters: cathodic pulse width 30, 60, 90, 120 µs, axon diameter (2–5 µm)	Anatomical target
	SciRun	FEM: field-axon (or Hessian matrix, Duffley et al., 2019)	User defined: any	User defined: any	User defined: any	May be combined with anatomical target and structural connectivity
Academic	Cicerone	Non-FEM LUT: based on Butson and McIntyre (2005b) and subsequent work	Monopolar (Medtronic 3387, 3389)	Electrode capacitance accounted for, isotropic homogenous tissue conductivity σ=0.3 S/m, user adjustable: encapsulation impedance	Cathodic monophasic, user adjustable: voltage or current amplitude, pulse width, pulse frequency	Anatomical target
	StimVision v2	Non-FEM: based on Chaturvedi et al. (2013) FEM: pathway activation, Howell et al. (2019)	Monopolar, multipolar and multi-monopolar (MDT 3387, MDT 3389, ABT 6172, BSN 2202)	Homogeneous isotropic σ=0.2 S/m, tissue encapsulation layer σ=0.1 S/m	Cathodic monophasic with built in effect of electrode capacitance; user adjustable: stimulus amplitude, pulse width	Anatomical target, structural network connectivity
Commercial	SureTune 4 (Medtronic)	Non-FEM LUT: based on Åström et al. (2015) data	Monopolar	Homogeneous isotropic σ=0.1 S/m	LUT VTA parameters: cathodic pulse width 30, 60, 90, 120 µs, axon diameter (2, 2.5, 3 µm)	Anatomical target, structural network connectivity
	Guide (Boston Sci.)	Non-FEM LUT: based on Butson and McIntyre (2005b) and subsequent work	Monopolar, Guide XT: directional	Electrode capacitance accounted for, isotropic homogenous tissue conductivity σ=0.3 S/m, user adjustable: encapsulation impedance	Cathodic monophasic, user adjustable: voltage or current amplitude, pulse width, pulse frequency	Anatomical target
	Vercise Neural Navigator with STIMVIEW XT (Boston Sci.)	Non-FEM LUT: based on 5.7 µm diameter fiber (MRG model) field-axon simulations, grid geometry	Monopolar, bipolar and directional (Boston Sci. leads)	Homogeneous isotropic σ=0.2 S/m, tissue encapsulation layer σ=0.1 S/m	Cathodic monophasic, incorporates electrode capacitance, user adjustable: current amplitude, pulse width	Anatomical target

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use of a server–client setup and computation via SciRun (Butson et al., 2013; Vorwerk et al., 2020).

As mentioned previously, the activating-function look-up-table method stemming from Butson and McIntyre (2005b) constituted the academic software Cicerone (Miocinovic et al., 2007), which was developed into the commercial tool, GUIDE, by Boston Scientific (Horn, 2017). StimVision is another academic software from the McIntyre lab that has versions stemming from Chaturvedi et al. (2013), the neural-network-based VTA predictor (Noecker et al., 2018), and most recently including the fast, pathway-activation model of Howell et al. (2019) and Noecker et al. (2021). The second version of StimVision uses the CIT168 human MRI brain atlas (Pauli et al., 2018) and the Petersen et al. axonal pathway models (Petersen et al., 2019) with patient-specific MRI information. It offers VTA estimations from a large variety of precomputed electrode configurations plus fiber activation using the Howell et al. (2019) driving-force predictor algorithm on modelled fibers in 9 general axonal pathways. It is a computationally efficient platform suited for detailed patient-specific modeling for retrospective or prospective clinical studies. SureTune is a commercial software package from Medtronic that provides VTAs in comparison to structural atlases and the ability to show fiber tracts for structural network connectivity with SureTune 4; it uses precomputed FEM data and visualizes estimated VTAs for 2, 2.5 and 3 μm fiber diameters for various stimulation amplitudes and pulse widths based upon data from Åström et al. (2015) and Johansson and Zsigmond (2021). Boston Scientific continues to incorporate more capability in their commercial software packages. The latest, Vercise Neural Navigator with STIMVIEW XT, is FDA approved and provides VTA estimation with co-visualization of anatomical targets for any monopolar, bipolar or directional electrode configuration for their DBS leads. Their platform allows for user input of stimulus current amplitude and pulse width and is based on precomputed data using field-axon (grid geometry) simulations following the methods of Butson and McIntyre (2005b) with FE model parameters of 0.2 S/m isotropic heterogenous brain tissue conductivity and 0.1 S/m for the tissue encapsulation layer (Malekmohammadi et al., 2022).

3 State-of-the-art in clinical studies

Over the last 10 years, many clinical DBS studies have been performed that use VTA methods with neuroimaging techniques to help define target sweet spots, understand the effect of current spread as it relates to unwanted side effects, and/or determine network activity to better define the mechanism of action, for example. This section details a sample of the insights gained by the community as a function of neurological disorders by such studies.

3.1 Parkinson's disease

Since Parkinson's disease (PD) was the first to be FDA approved for DBS therapy, this disease has ostensibly the most studies for it regarding DBS effectiveness, and thus an interesting progression of model-informed insight can be seen. An early study by Maks et al. showed that through patient-specific VTA simulation with methods stemming from Butson and McIntyre (2005b) and Butson et al. (2007) a region of the dorsal STN including white matter tracts dorsal to that region was correlated with improvement in overall motor symptoms based upon the Unified Parkinson's Disease Rating Scale (Maks et al., 2009). Alberts et al. and Frakenmolle et al. then showed decent propensity for using VTA-modeling for prospective DBS programming (i.e., stimulus amplitude and pulse width) via small-cohort studies that assessed patient therapeutic scores with and without VTA-based programing settings maximized for overlap with the regions found in Maks et al. (Alberts et al., 2010; Frankemolle et al., 2010). Both of those studies also addressed reduced cognitive function as a side-effect of non-optimal stimulation. Other studies used VTA overlap with anatomical structures to assess verbal fluency in STN DBS (Åström et al., 2010; Mikos et al., 2011) and with DBS in the globus pallidus (GP) (Dietz et al., 2013).

With the addition of more sophisticated combinations of VTA and neuroimaging, targets were better defined, and networks associated with optimal therapy and side effects were identified. The first study that defined the method of probabilistic stimulation mapping of a cohort of patient-specific VTAs, albeit made from normative structural atlases (Butson et al., 2011) reinforced the results of Maks et al.; and they defined further specificity between improvements in rigidity and bradykinesia as a function of spatial regions in the STN. Vanegas-Arroyave et al. performed a seminal study that used DTI tractography and VTA to give network-based information on the mechanism of action of therapeutic STN DBS (Vanegas-Arroyave et al., 2016). They used patient-specific tractography from 3 T MRI of all 22 patients and the simple, non-FEM VTA method of Mädler and Coenen (2012) and surmised that the dentato-rubro-thalamic tract, zona incerta and/or pallidothalamic tract directed towards the thalamus contributed to clinically effective DBS based upon the therapeutic window established during monopolar review. Another study assessing structural connectivity via tractography and VTA looked for the network effect of speech disturbances in STN DBS (Mahlknecht et al., 2017). Their VTA and neuroimaging modeling done via SureTune (Medtronic, MN) was used to depict overlap of corticospinal and corticobulbar tracts. The corticospinal and corticobulbar tracts in this study were derived from patient-specific tractography and then averaged across the group. This information was leveraged to determine that the activation of the internal capsule was inversely correlated with the resting motor thresholds of the contralateral orbicularis oris muscle and first dorsal interosseus muscle, in the face and the hand, respectively (Mahlknecht et al., 2017). Horn et al. then perfromed a study of both structural and functional network-connectivity seeded by VTA for STN DBS (Horn et al., 2017). They used the FEM-based VTA model available in Lead DBS at a threshold value of 0.2 V/mm with tractography either from a normative connectome generated from a large database of healthy subjects or a normative connectome generated from a database of 90 PD patients matched for sex and age. They showed that connectivity results were similar with both the healthy and PD connectomes and that effective STN DBS largely echoed the results found in Vanegas-Arroyave et al. More specifically, the supplementary motor area (SMA), anterior cingulate, and medial prefrontal cortex were correlated with effective DBS for overall motor improvement, while M1 was negatively correlated. Their study also paved the way for probabalistic network-based atlases made from large populations in retrospective studies. Importantly, their study also showed that the connectivity profiles (or network-based atlases) derived from one cohort could be used to predict clinical efficacy in independent

cohorts. Around the same time, Akram et al. perfromed a study that used SureTune-derived VTAs and a voxel-wise statistical approach for a target-based probabilistic stimulation map and structural connectivity analysis for STN DBS. The tractography was patient-specific and they surmised the following details: the central portion of the superior STN is most effective for tremor, while stimulation in medial and posterior areas, within the superior portion, gives highest improvements in bradykinesia and rigidity; also connectivity to M1 appears to predict improvement in tremor, SMA predicts improvement in bradykinesia, and both SMA and the prefrontal cortex (PFC) predicts improvement in rigidity (Akram et al., 2017). Of note, Dembek et al. later proposed a "sweet spot" slightly more dorsal and lateral than that of Akram et al. using a similar voxel-wise statistical approach for probabilistic mapping with VTA estimations via the Lead DBS framework using a FEM-heuristic approach with heterogenous tissue conductivity for white and grey matter and an electric field threshold value of 0.2 V/mm and was also able to cross-validate this model in a completely independent second cohort (Dembek et al., 2019). During cross-validation, the model was found to explain 20% of the variance in motor score improvement in the independent cohort ($p < 0.001$). Another study used non-atlas-based patient-specific VTA estimation for voxel-wise probabilistic stimulation maps of DBS efficacy for PD (Malaga et al., 2021). Using true patient-specific MRIs for structure segmentation and anisotropic conductivity they calculated VTAs via electric-field threshold values as a function of stimulation parameter given by Åström et al. (2015) and mapped optimal stimulation locations to be regions dorsomedial to the STN, near the posterior half of the nucleus.

Lin et al. performed a study with patient-specific tractography and non-FEM VTA via Lead-DBS and used machine learning (random forest classifiers) to characterize specific connectivity features with DBS outcome (Lin et al., 2020). They found the thalamus, hippocampus, pallidum, M1, SMA, and the superior frontal gyrus (SFG) all corresponded with effective DBS contacts. Additionally, the concept of using machine learning to classify and/or provide a predictive model for DBS effectiveness based on VTA-based neuroimaging data is a topic of interest and has been implemented for STN DBS in another recent study (Chen et al., 2022). Other recent work use VTA-seeded connectivity maps to take closer look at side effects including depression in STN DBS (Irmen et al., 2020), stimulation-induced dysarthria (SID) during STN DBS (Dayal et al., 2020), and SID in GPi/GPe DBS (Tsuboi et al., 2021).

There are fewer studies using pathway activation models in the literature, but they pose to give more nuanced information on the mechanism of action. Butenko et al. suggest using PAM to define a profile of pathways whose balanced activation alleviates the profile of symptoms (Butenko et al., 2022). Their study results show that is not key to activate/modulate a single specific tract (such as the hyperdirect pathway alone) but instead a specific array of tracts connecting or passing the STN including the pallidothalamic projections: the ansa lenticularis and lenticular fasciculus (Butenko et al., 2022).

3.2 Essential tremor

DBS programming for tremor suppression in essential tremor (ET) is one of the most straightforward procedures in neuromodulation. There is direct visual feedback for tremor suppression that responds in real time (on the order of seconds) to guide DBS programmers. However, the challenge in DBS for ET lies in maximizing tremor suppression while minimizing stimulation induced side effects. Here, several groups have tried using VTA models to solve this task. For example, similar to Tsuboi's characterization of stimulation induced dyskinesia in PD, Petry-Schmelzer et al. sought to determine the brain network fingerprint of stimulation induced dysarthria in ET patients as well as build a predictive model for stimulation related speech intelligibility after thalamic DBS (Petry-Schmelzer et al., 2021). FEM-based VTAs were used to evaluate structural connectivity using a discriminative fiber tract analysis within a normative connectome. The model was able to demonstrate that 64% ($p < 0.001$) of the variance resulting from stimulation induced speech unintelligibility could be explained by the identified fibers (Petry-Schmelzer et al., 2021). The authors also found that the majority of stimulation induced dysarthria was associated with motor cortex or cerebellar modulation. This study highlights the capability of using VTA to create fiber filtering algorithms that can identify brain networks implicated through stimulation.

Target-based probabilistic stimulation maps derived by VTA modeling have shown potential in reducing the clinical programming and optimization for DBS in ET and in assessing optimal targets for side-effect suppression. Åström et al. explored how VTA models could be leveraged to predict effective electrode contacts when specifically targeting the caudal zona incerta (Åström et al., 2018). Åström et al. created atlas-based FEM-based VTA models coupled with an axon cable model in an isotropic, homogenous tissue medium (Åström et al., 2018). The VTA-based model was able to predict the exact clinical contact 60% of the time and match within the top 2 options 83% of the time. In a recent study, Malaga et al. show that added patient specificity by using patient MRI DTI data for defining the microstructure of the brain regions instead of atlases and unique DTI-informed tissue conductivity to generate the VTAs for probabilistic stimulation mapping helped explain undesirable side effects (Malaga et al., 2023). They used an FEM-heuristic VTA model with threshold of 0.2 V/mm and found that the patient-specific structure-based VTA performed better than atlas-based VTA prediction in explaining sustained paresthesia. 94% of the patient-specific VTAs overlapped with sensory thalamus estimates compared to only 74% of the atlas-based VTAs.

VTA-based predictive models have also been utilized to refine surgical precision and predict therapeutic outcomes. Middlebrooks et al. employed FEM-derived VTA models within a normative connectome framework to derive structural connectivity indices for 97 ET patients undergoing unilateral thalamic DBS (Middlebrooks et al., 2021). These indices, derived from VTA modeling, facilitated the creation of a unique spatial connectivity "fingerprint" for each subject, which was then applied in a leave-one-out cross-validation scheme to prognosticate the percentage of tremor reduction post-DBS. The connectivity "fingerprint" demonstrated a significant correlation with tremor suppression ($R = 0.41$, $p < 0.0001$) and robustly predicted outcomes in a completely independent cohort of 14 ET patients ($R = 0.59$, $p = 0.028$). Subsequent analysis of the model indicated that the neural regions most indicative of tremor suppression coincided with the dentato-rubro-thalamic tract (DRTT). The authors concluded that the DRTT can be leveraged as an anatomic region of interest for future tremor intervention.

3.3 Epilepsy

Medication refractory generalized epilepsy is another challenging field that has benefited from VTA analyses to guide neuromodulation therapy. Although many brain networks such as the default mode network (DMN) have been implicated, identifying a common epileptic origin remains elusive and difficult (Cataldi et al., 2013). Previous electrophysiology studies have suggested that epileptic pathogenesis may originate from the centromedian nucleus of the thalamus (CM) and be modulated by the anterior nucleus of the thalamus (ANT). DBS of these targets have shown promise in clinical trials but there remains significant variability in seizure outcomes (Salanova et al., 2015). Several studies have employed VTA based models to test these hypotheses and explain the variance seen in clinical studies. Middlebrooks used FEM-based VTAs (using 0.2 V/mm threshold for activation following Horn et al., 2017) from 6 patients with refractory epilepsy as seeds for a functional connectivity analysis within a normative connectome to try to explain the variability in seizure response after ANT DBS (Middlebrooks et al., 2018). This method revealed that 3 patients who were strong responders, defined as seizure frequency reduction by at least 50%, had much stronger connectivity to the DMN compared to the other 3 patients who did not have a strong response after ANT DBS. Similarly, Torres Diaz et al. conducted an FEM-based VTA study (using 0.2 V/mm threshold for activation following Horn et al., 2017). They incorporated both structural and functional connectivity mapping in 10 patients with generalized epilepsy who received CM DBS (Diaz et al., 2021). By using the VTA as a seed for both patient-specific diffusion MRI and normative resting state fMRI, Torres Diaz et al. identified a well-delineated network comprised of sensorimotor and supplemental motor cortices, the brainstem, and cerebellum that correlated with the greatest seizure reduction. Interestingly, both structural and functional connectivity analyses converged to a similar network, illustrating how VTA-based network analyses can refine the region of interest for targeted neuromodulation. However, the use of non patient-specifc VTA modeling in these studies may not accurately capture the axonal modulation in these dense thalamic nuclei and this effect may be further amplified using a normative connectome. Charlebois addressed this issue by employing an enhanced VTA model using FEM based upon electrical conductivity derived from patient specific DTI sequences and incorporating an encapsulation area around the lead. Additionally, they utilized activation function thresholds that were obtained from biophysical field axon models which are derived from stimulation parameters (following methods in Butson and McIntyre, 2007 and Duffley et al., 2019). These VTAs were used as seeds for structural connectivity analyses across both a normative connectome and patient-specific connectome in 22 patients implanted with an RNS neurostimulator (NeuroPace, Mountain View, CA) (Charlebois et al., 2022). Through this technique, Charlebois found that there was no significant correlation between the normative connectivity map and seizure reduction ($r = 0.28$, $p = 0.09$), but there was a significant correlation between the patient-specific connectivity map and seizure reduction ($r = 0.74$, $p < 0.0001$). These studies provide an excellent showcase of the impact VTA and tractography model selection has on connectivity results and how factors such as disease pathology and network complexity may play a role in how connectivity studies should be designed in the future.

3.4 Dystonia

While DBS for dystonia can be incredibly effective, the time course for improvement can be highly variable and up to 25% of patients may be non-responders (Isaias et al., 2009; Volkmann et al., 2012). Although there is a consensus to target the motor region of the GPi, the degree of variability in patient outcomes necessitates an urgent need to better understand neuromodulation in dystonia. Cheung combined FEM-based field-axon VTA models (following Butson et al., 2007) into a target-based probabilistic stimulation atlas to map the optimal regions of stimulation in GPi DBS for dystonia (Cheung et al., 2014). Patient-specific VTAs were transformed into normalized template space and thresholded to include only voxels that provided at least 75% improvement and were shared by at least 75% of the cohort. This technique identified a region in the center of the posterior portion of the GPi that was associated with the greatest dystonia improvement. This study demonstrates how VTAs can be used to guide DBS targeting from a broad spatial perspective and characterize general anatomic trends/relationships. As the authors cautioned, however, this technique was designed to simulate the region of influence from DBS therapy and makes no assumptions regarding disease specific pathology or patient specific connectivity. It is simply aimed to define the anatomic regions most frequently modulated by DBS. Reich et al. expanded on this approach and used FEM-based VTAs (via SureTune), methods from Åström et al. (2015), which used homogenous isotropic conductivity as well as a single cable axon model to create a target-based probabilistic stimulation atlas from a much larger cohort of 105 patients (Reich et al., 2019). This atlas was also transformed into normalized template space but identified a different region compared to Cheung et al.—the ventroposterior GPi as well as the surrounding white matter tissue. Although the authors offer several explanations for these differences, including limitations of image processing and the use of voxel-wise statistics rather than a threshold, this also highlights the limitations of FEM-based VTAs being used as a static approximation of the DBS electric field and converting this information into a 3D volume. The authors rightly point out that using VTAs in this manner would highlight a "volume" of neural tissue rather than a "target." However, later work by the same group (Soares et al., 2021) using predictions based on the same computational methods corroborated the ventroposterior GPi as the target sweet spot for isolated dystonia and combined dystonia patients. Their study also stated that only 32% of the variance in patient outcomes could be predicted by their model and cautioned that this type of model alone would not be sufficient for clinical prediction.

3.5 Obsessive compulsive disorder

VTA-seed-based connectivity maps have also been used in OCD DBS to guide the target selection and DBS programming optimization processes. As OCD is a heterogenous condition and thought to be a neurologic disorder that results from multiple overlapping dysfunctional neural networks, connectivity mapping has emerged as a useful to tool to highlight regions of interest that

are most associated with clinical improvement. As most clinical trials in OCD DBS typically have less than 20 patients, many connectivity studies employ the use of normative connectomes as a foundation for their analysis. In scenarios where the study population is limited, the strength of VTA seeding within a normative connectome is highlighted as patient-specific tractography of a small cohort would otherwise be too noisy to interpret. Baldermann and Li both used FEM-based VTA (Lead-DBS and/or SureTune) structural connectivity analyses within a normative connectome to illustrate that specific connectivity profiles could be generated that predict clinical outcomes (Baldermann et al., 2019; Li et al., 2020). Both studies detected relevant fiber tracts within the anterior limb of the internal capsule that led to the identification of a unified hyper direct pathway connecting the dorsal anterior cingulate cortex to the anteromedial subthalamic nucleus. Li further challenged the generalizability of this model by cross-predicting clinical outcomes from completely independent cohorts from other institutions. Gadot combined the results of the FEM-based VTA (via Lead-DBS) connectivity with discriminative fiber tract analysis to predict the clinical outcomes of another independent cohort of 10 patients in a rank-based fashion (Gadot et al., 2023). Gadot's model was able to accurately predict the ranked order of improvement in the 10 patients (Spearman correlation $r = 0.75$, $p = 0.013$), demonstrating the utility of VTA based models even within normative connectomes.

4 Discussion

4.1 General themes and limitations

Within specific neurological disorders, the use of VTA-informed neuroimaging to suggest sweet spots for DBS targets and/or activation of connected fiber tracts that innervate distant cortical and subcortical regions has advanced the field of DBS neuromodulation. Generally, the field has adopted the use of retrospective clinical data to make VTA-informed models of target or network-based maps that quantify the probability of effective patient outcome (i.e., probabilistic stimulation atlases) to provide more insight on the condition and in some cases to predict patient efficacy in independent patient cohorts based on lead placement and DBS parameters. However, despite the added benefit these data-driven models have provided, the models cannot fully explain the degree of variability in clinical outcomes.

Limitations to the modeling techniques that contribute to error come from uncertainties in both the neuroimaging side of modeling as well as the VTA/pathway activation side. On the imaging side there is inherent error in the following methods: co-registration of DBS leads from pre-and post-operative brain MRI or CT scans, warping of established atlases of target brain structures to individual patients, using a normative structural atlas or connectome versus patient-specific microstructure and fiber tract information, and DTI-based tractography estimation (e.g., probabilistic or deterministic). On the VTA side, one obvious source of error is that the volume defined by the VTA is unphysical as the true spatial nature of the axon pathways are not included. Gunalan et al. showed that when comparing pathway-activation models to VTA models that calculated fiber-tract overlap to define structural network connectivity, there was a large discrepancy between the results (Gunalan et al., 2018). Further, if the VTA is assumed to provide a good estimate of spatial activation, then differences within the parameters chosen for FEM-based VTAs can also contribute to variation. The parameter choices include using isotropic, anisotropic, homogeneous, and/or heterogenous tissue conductivities (whose values for specific materials may vary between studies), modeling a high resistive encapsulation region around the lead or not, modeling the capacitive effects of the electrode interface and time nature of the stimulus pulse trains including frequency or not, and the choice to use heuristic threshold levels or one derived or defined by axon models add variation and error in the final model.

Regarding FEM-based models, the choice of how to model the brain tissue with respect to electrical conductivity has seen much variation in the literature. Early on, it was shown that inclusion of a high resistivity tissue encapsulation area adjacent to the DBS lead in isotropic tissue models made significant changes to the resulting VTA (Butson et al., 2006). In later studies, tissue anisotropy was evaluated via pathway activation models of neural axons. Chaturvedi et al. showed that anisotropy of the tissue outside the encapsulation region, as defined by local DTI-informed conductivity tensors will further influence (i.e., a reduction of the spatial extent of axonal activation), which more closely matched clinical estimates of stimulation (Chaturvedi et al., 2010). Additionally, Howell and McIntyre compared models of heterogeneity (i.e., white and grey matter), anisotropy, and frequency effects to isotropic homogeneous conductivity models and found that inclusion of anisotropy had the largest effect followed by heterogeneity (Howell and McIntyre, 2016). They also showed that different methods to compute anisotropic conductivity tensors, with methods that did or did not incorporate influence of a measured load impedance (i.e., electrode interface effects), resulted in differences in neural activation prediction. Moreover, dielectric dispersion (i.e., modeling a complex conductivity, $\sigma + j\omega\varepsilon$) had the smallest effect (<1% mean average difference) within anisotropic models. In their study, a tissue encapsulation region was present in the isotropic cases but not in the others. In a recent study, Liu et al. show how patient-specific anisotropic tissue conductivity in VTA-based models contribute to significant patient variation across a cohort of 40 patients as well a significant deviation from isotropic conductivity-based models (Liu et al., 2024). Out of the three commercial software platforms listed in Table 1, all use homogeneous isotropic brain tissue with three different values for conductivity and only two (Guide and Vercise Neural Navigator) incorporate a tissue encapsulation layer. One more aspect to point out, the complexity of the volume conductor of the head model and its grounding scheme for monopolar stimulation can also contribute to differences in voltage field calculations and thus VTA or pathway activation results especially if the overall impedance value measured via the IPG is used to tune the model (Grant and Lowery, 2009).

Regardless of all of these model-specific variabilities, one aspect to point out is that if neuroimaging methods use average information from population groups and normative structural atlases or connectomes for probabilistic maps, we believe that the extent of VTA specificity (e.g., FEM or not, field-axon or heuristic threshold, etc.) will have less of an effect on the variation of the outcome prediction

by such a model, as the variability due to averaging across a population may be larger than variability introduced in VTA methodologies. Moreover, modeling studies that use atlases for determination of DTI-based conductivity tensors in FEM VTA or PAM predictions in retrospective studies could erroneously alter the local conductivity for a specific patient and thus add error to the group-based probabilistic map. For true patient-specific applications, the choice of the mentioned model parameters will likely contribute a great deal to the accuracy of the VTA or pathway activation prediction.

Regarding the use of VTA-informed neuroimaging methods (i.e., target vs. connectivity-based), it is interesting to see that within the different disorders, some modeling paradigms are more consistently used than others. For PD and ET both target-based and network-based probabilistic stimulation mapping have been used by the community and some combine both methods (Akram et al., 2017; Tsuboi et al., 2021). On the other hand, recent work on dystonia has been focused on target-based analyses and not network/connectivity to fine tune the sweet spots for stimulation in the GPi, leading to question if differences in target results by different groups could be resolved with the addition of network-based mapping used in conjunction. And recent studies for epilepsy and OCD have only used VTA-based network/connectivity mapping to provide insight. Pathway activation models that provide information on network connectivity are seen even more seldom in the literature, potentially because of the computational complexity of the method.

4.2 Future of neuromodeling for DBS

Understanding the brain within the context of neurological disorders and neuromodulation therapy is clearly challenging and subject to many individual idiosyncrasies; however, it is impressive how VTA-based neuromodeling, regardless of the VTA method, has been able to provide added detail for target sweet spots, regions of fiber tracts that correlate with unwanted side effects, and more insight into the mechanism of action for effective DBS with much consensus between multiple studies. One of the key features that is apparent in the literature is the notion that predictive models can be garnered from population/group results of retrospective studies for a particular disorder. The extent to which those models (probabilistic stimulation atlases, target-and/or network-based) need to be fine-tuned for a more precise predictive model is a question yet to be answered. Recent work by Johnson et al. show that the added specificity of pathway-activation models with patient-specific structural connectivity analysis yielded robust metrics for prediction of patient outcome for GPi DBS for Tourette syndrome, which is a disorder that has had high variability of patient responses to DBS treatment (Johnson et al., 2021). Also, Hollunder et al. suggest a paradigm shift in how group-based atlases are used for the end patient (Hollunder et al., 2022). They suggest the creation of network-based atlases/templates from population studies for the disease symptom (e.g., tremor, rigidity, cognitive flexibility, anxiety) rather than just the disease, and then those templates can be added together to create guidance for personalized DBS target and stimulation. And the recent work by Malaga et al. promotes the use of patient-specific microstructure (vs. atlas-based) in addition to patient-specific tissue conductivity to create better informed target-based probabilistic stimulation atlases (Malaga et al., 2021, 2023).

Modeling of tissue activation coupled with neuroimaging techniques form the computational basis for predictive models generated from group retrospective studies as well as for establishing the patient baseline data for personalized medicine that makes use of predictive models. The degree to which the predictive model is accurate for an individual should be highly influenced by the level of patient accuracy of the data from the tissue activation/modulation model and the neuroimaging methods (e.g., for generation of brain structures and fiber pathways). New retrospective studies that will generate target-based or network-based probabilistic stimulation maps might indeed benefit from more accurate patient-specificity for brain structures and fiber tracts. Innovation in DTI-based methods would serve to increase model accuracy. If patient-specific parameters are used for target-based studies, then the VTA method should also be most accurate/specific and employ field-axon simulations, which are dependent on stimulation parameters, rather than field-heuristic or non-FEM VTA models. Moreover, there is a lack of clinical comparative studies that evaluate the influence of PAM vs. VTA-based network connectivity mapping, for example. The field would be greatly served if more comparative studies using different neural activation/modulation approaches were performed.

Furthermore, it is essential to validate the strength and general applicability of these models through carefully planned and extensive prospective clinical trials. Conducting such trials is vital for establishing credibility with clinicians, which in turn, will promote the incorporation of these models into routine clinical practice.

Author contributions

EP: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. CF: Conceptualization, Writing – original draft, Writing – review & editing. DP: Writing – original draft. JC: Writing – original draft. AP: Writing – original draft. HS: Writing – original draft. JW: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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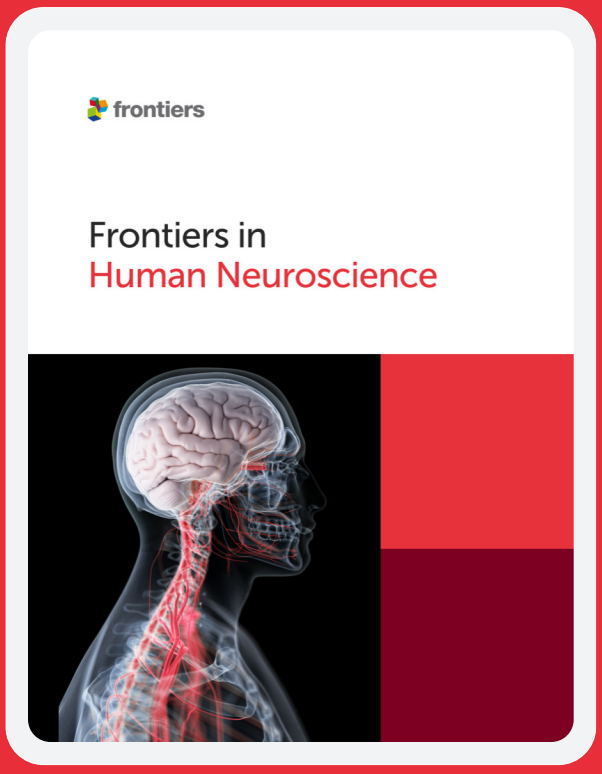

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